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AMERICAN HEART JOURNAL

AN INTERNATIONAL PUBLICATION FOR
THE STUDY OF THE CIRCULATION

American Heart Journal

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THE ETIOLOGY OF CARDIAC ENLARGEMENT IN CORONARY OCCLUSION, HYPERTENSION, AND CORONARY ARTERY DISEASE

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INTRODUCTION

THE production of cardiac enlargement, in patients who suffer from coronary artery occlusion, has hitherto generally been attributed to hypertension either directly[1-11] or indirectly.[1,6,9,12-15] Occasionally, the cardiac enlargement was attributed to coexisting coronary artery disease and hypertension[5] or to coexisting hypertension and heart failure.[5,7,9] Smith and his associates[11] stressed the importance of the severity of the hypertension as an etiologic factor in enlargement of the heart. Gross and Lisa[10] believed that coronary artery disease was an insignificant factor in the causation of cardiac enlargement, thus indirectly implying that hypertension played an important role. Some writers held that neither coronary artery disease alone[16-19] nor myocardial infarction[20] could of themselves cause an increase in the size of the heart.

A lesser number of authors have maintained that coronary sclerosis, in the absence of hypertension, did produce cardiac enlargement.[13,14,21-24] Others believed that myocardial infarction,[24-28] myocardial "damage",[13,29] myocardial "injury",[30] or heart failure alone[12,24,31] could, in the absence of increased arterial tension, cause enlargement of the heart in patients suffering from coronary occlusion.

From a review of the extensive literature on the subject, it is obvious that the majority consider hypertension to be an essential factor in the causation of an enlarged heart, in cases with coronary occlusion. A clear, dissenting minority, however, does exist. Because of this diversity of opinion, because of the basic and clinical importance of the subject, and because all the conclusions reached hitherto were based on an erroneous definition of hypertension, and were, therefore, obviously untenable, it seems advisable to reconsider the entire problem.

Since the blood pressure does normally increase with age and does vary with sex,[32-34] both the age and the sex of each patient must be taken into account before the presence of hypertension can be definitely established and before conclusions concerning its effects on the size of the heart can be drawn.

Such correct definitions of hypertension have, hitherto, not been available. In order to establish the range of normal blood pressure and to define the limits of hypertension, Master and associates,[23,24] recently analyzed the blood pressure of many thousands of working people, between the ages of 16 and 65 years. With their newly established limits of hypertension, an attempt has been made to determine whether hypertension alone or coronary artery disease alone causes the cardiac enlargement found in cases of coronary occlusion.

The heart was considered to be "enlarged", when its total transverse diameter was unequivocally more than one-half of the total internal thoracic diameter, measured at the level of the dome of the diaphragm. The shape and general silhouette of the heart were also studied before the diagnosis of cardiac enlargement was made. In every case, it was clearly evident that the total transverse diameter of the heart, as well as its area and volume, were enlarged. The Clark-Ungerleider tables[35] served as a further check on the determination of the size of the heart.

MATERIAL

Six hundred patients, 16 to 65 years of age, who suffered from coronary occlusions were studied. We limited ourselves to this age group simply because the blood pressures of people, 16 to 65 years old, gainfully employed, had been the basis of the statistical analysis of blood pressure ranges.[22,33,34] Of these, 500 were men and 100 were women. Of the 500 men patients, the largest group (25.6 per cent) was between the ages of 50 and 54 years; the next largest group (23.0 per cent) was 55 to 59 years of age; 17.9 per cent were 45 to 49 years old; 15.4 per cent were 40 to 44 years old, and 12.6 per cent were between 60 and 64 years of age. Thus one-half of the men were 50 to 60 years old.

This age seems to be the dangerous decade for the occurrence of coronary occlusion among men who are less than 65 years old. Nevertheless, nearly two-fifths (38.8 per cent) of the patients were under 50 years of age.

Among the men seventy-seven (a few less than one-sixth of the patients) had definitely enlarged hearts, an incidence of 15.4 per cent (Table I). About twenty borderline cases of cardiac enlargement were not included. In these, the transverse diameter of the heart was just about 50 per cent of the total thoracic diameter.

The frequency of enlargement of the heart increased moderately at the age of 55. Thus, among the patients who were 55 to 59 years old, the incidence of cardiac enlargement was 19.1 per cent, whereas the average incidence was 15.4 per cent. The incidence in those who were 60 to 64 years old was still higher—27 per cent. The number of cases is too small to allow definite conclusions to be drawn, but it appears that there is an increased incidence of cardiac enlargement at the age of 55, and that there is a definite increase at the age of 60. This was found in patients with hypertension as well as those with normal blood pressure.

Hence "age", or coronary atherosclerosis, which is concomitant with the aging process, causes enlargement of the heart in those who have sustained a coronary occlusion.

It is obvious that the blood pressure readings prior to the onset of the coronary occlusion were the observations that were employed.   The blood pressure falls following acute coronary occlusion and therefore cannot be used in a study such as we have undertaken.

Enlargement of the heart, in men with coronary occlusion, occurs in the absence of hypertension.   Of our 500 patients, forty-five had normal blood pressure and enlarged hearts.   Of these, sixteen had had heart failure, and twenty-nine had never been in heart failure.   Two of the latter had valvular heart disease as well as arteriosclerosis.   Hence the presence of heart failure or hypertension is not essential for the production of cardiac enlargement.   It, therefore, appears that coronary sclerosis alone, without hypertension, can produce cardiac enlargement.

Sixteen cases of ventricular aneurysm were found among the forty-five patients with cardiac enlargement whose blood pressure was normal.   The ventricular wall in these cases was weakened sufficiently so that a paradoxical pulsation resulted.   Apparently, normal blood pressure does not preclude the development of ventricular aneurysm, nor does hypertension predispose patients to it.   Of the twenty-nine cases of hypertension with cardiac enlargement, eight had a ventricular aneurysm, (27.6 per cent); of the forty-five cases of normal blood pressure with cardiac enlargement, sixteen had a ventricular aneurysm, (35.5 per cent).   Coronary artery disease and/or myocardial infarction, therefore, can produce not only an enlarged heart but also a weakening of the wall of the left ventricle.

The frequency of cardiac enlargement among the 136 hypertensive patients (Table I) was 21.3 per cent.   Among those whose blood pressure was normal (332 cases), it was 13.6 per cent.   At all ages, cardiac enlargement was most frequent among those with increased blood pressure.   It seems clear, from these findings, that hypertension is an important factor in the causation of the cardiac enlargement.

At the age of 60, enlargement of the heart was present in more than one-third of the cases with hypertension, 36.8 per cent.   The incidence of enlargement of the heart increased sharply at that age and also at the age of 55, even in those with normal blood pressure.   Hence, advancing age, with its concomitant coronary sclerosis, is apparently also an important cause of enlargement of the heart in patients who suffer from coronary occlusion.

Whether coronary sclerosis or hypertension is the more important factor in the production of cardiac enlargement, has not, as yet, been clearly determined. However,the frequency of cardiac enlargement is greatest when both coronary sclerosis and hypertension occur together, e.g., in the 60 to 64 year age group.

Cardiac enlargement does occur in the presence of coronary sclerosis alone; it occurs most frequently (in about 40 per cent of the cases of coronary occlusion) when hypertension and coronary sclerosis (the aging process) are both present.

TABLE I. CORONARY OCCLUSION IN 500 MALES: BLOOD PRESSURE AND ENLARGEMENT OF THE HEART (EH)

	TOTAL CASES			HYPERTENSION			BORDERLINE			NORMAL		
	NO.	NO. EH	(%) EH	NO.	NO. EH	(%) EH	NO.	NO. EH	(%) EH	NO.	NO. EH	(%) EH
All ages (25-64)	500	77	15.4	136	29	21.3	32	3	9.4	332	45	13.6
25-39	27	2	*	6	1	*	1	0	0	20	1	*
40-44	77	7	9.0	20	4	20.0	3	0	0	54	3	5.6
45-49	90	13	14.5	23	5	21.7	5	0	0	62	8	12.9
50-54	128	16	12.5	35	5	14.3	6	0	0	87	11	12.7
55-59	115	22	19.1	33	7	21.2	10	2	*	72	13	18.1
60-64	63	17	27.0	19	7	36.8	7	1	*	37	9	24.3

*Less than 3 cases, per cent not calculated.

TABLE II. CORONARY OCCLUSION IN 100 FEMALES: BLOOD PRESSURE AND ENLARGEMENT OF THE HEART (EH)

	TOTAL CASES			HYPERTENSION			BORDERLINE			NORMAL		
	NO.	NO. EH	(%) EH	NO.	NO. EH	(%) EH	NO.	NO. EH	(%) EH	NO.	NO. EH	(%) EH
All ages (35-64)	100	44	44.0	71	37	52.2	8	2	*	21	5	23.8
35-49	22	5	22.6	14	4	28.6	2	1	*	6	0	0
50-54	18	5	27.8	14	5	35.8	0	0	0	4	0	0
55-59	28	12	42.9	18	8	44.4	3	0	0	7	4	57.2
60-64	32	22	68.8	25	20	80.0	3	1	*	4	1	*

*Less than 3 cases, per cent not calculated.

Among the 100 women studied, coronary occlusion occurred at a later age than among the men. The highest incidence (thirty-two cases) occurred in those between the ages of 60 to 64; twenty-eight patients were 55 to 59 years old; eighteen were 50 to 54 years old. Thus, 60 per cent of the episodes of coronary occlusion among women took place after the age of 55, whereas barely 22 per cent of the attacks among women occurred under the age of 50.

Among the 100 women, enlargement of the heart was found 44 times (44 per cent, Table II). The frequency of cardiac enlargement among women was three times as great as it was among men—44 per cent versus 15.4 per cent. This higher frequency of cardiac enlargement among women was found among those with hypertension (women 52.2 per cent and men 21.3 per cent, Tables I and II) as well as among those with normal blood pressure (women 23.8 per cent and men 13.6 per cent). Since 71 per cent of all women studied were hypertensive, whereas only 27 per cent of the men had hypertension (also a ratio of 3 to 1), it is obvious that hypertension is the most important factor in the causation of enlargement of the heart in women.

Cardiac enlargement may occur among women in the presence of coronary sclerosis alone, also, as it does in men. Among the twenty-one women whose pressure was normal, five (23.8 per cent) had enlarged hearts. It occurs more frequently among women in the presence of hypertension alone (52.2 per cent). It occurs most frequently (61.1 per cent), as it does in men, when coronary sclerosis and hypertension are both present.

DISCUSSION

Previous investigators who studied the association of hypertension and enlargement of the heart, as in the study of hypertension and other clinical entities, employed only one blood pressure limit for their definition of hypertension, no matter what the age or sex of the person. We ourselves had fallen into this error for many years. It is obvious that with ages 30 years and more, with which studies similar to this one have dealt, a single definition of 140/90 mm. Hg, or 150/100 mm. Hg, or even 160/100 mm. Hg and more is illogical. In the younger ages those blood pressures may be abnormally high, whereas in men and women of 60 years or more these limits may be quite normal. We could literally cite scores of references in which one limit of blood pressure was the sole criterion for hypertension, no matter the age or sex of the patient.[36] Thus, in a very recent follow-up study of nearly 7,000 men and women suffering from angina pectoris the limit for increase of arterial tension was a blood pressure of 150 mm. Hg or more systolic and/or 90 mm. Hg or more diastolic for all, in spite of the fact that the youngest patient was 28 and the oldest 92! Thus, in an otherwise most excellent investigation, the authors unconsciously perpetuated a common mistake.[36]

The mechanism of the development of an enlarged heart in coronary artery occlusion in the absence of hypertension is a fundamental one. Our study reveals that an enlarged heart often appears in coronary disease without previous hypertension and also without gross heart failure. Enlargement frequently occurs, simply and definitely, in the presence of coronary artery disease alone.

The cause of this is obscure but in arteriosclerosis of these arteries there is anoxemia of the myocardium. This is as far as we can go for explanation at the present time; the intrinsic pathogenesis of the increase in size of the heart in coronary sclerosis can only be speculative. Those interested may consult our references and a recent paper by Grant,[37] who presents a comprehensive bibliography on "cardiac hypertrophy."

A word should be said about mechanism of "ventricular aneurysm". This type of cardiac enlargement is classically associated with coronary occlusion and frequently with hypertension. We did not employ the term in the customary sense of an eccentric bulge in the left ventricle. We employed the expression to connote a heart, clearly enlarged, with a reversal of pulsation during systole as observed on fluoroscopy, and by roentgenkymogram when the latter procedure was used. The ventricular contraction was "paradoxical", that is, during systole the involved wall passively dilated, whereas the remainder of the left ventricle contracted normally. Since these instances of cardiac aneurysm were often cases with the largest hearts and since physicians so often assume that hypertension is frequently associated with both huge hearts and often also with "ventricular aneurysms", we were especially interested to study the incidence of high arterial tension in this type of heart. The increase in size of the heart very frequently occurred in the presence of normal blood pressure. Coronary sclerosis with its anoxemia of the myocardium must be the prime reason for the enlargement in ventricular aneurysm. Very severe coronary sclerosis is usually found at post mortem.

Although we have demonstrated that enlargement of the heart took place in patients who had had coronary artery occlusion but a "normal" blood pressure prior to the acute episode, it may be that even normal arterial tension, if sustained, particularly to the age of 50 to 54 years in men and to the age of 60 to 64 years in women, causes coronary sclerosis and/or cardiac enlargement. This has been the thesis of Moschcowitz.[38] According to his conception, one would conclude that the division of blood pressure into normal and hypertensive limits was an unnecessarily artificial one, and Moschcowitz could argue that the observations in this paper confirmed his theory since enlargement of the heart was found both in the presence and in the absence of hypertension.

It is our opinion that although cardiac enlargement is observed in the presence of normal blood pressure, that nevertheless hypertension, when present, is an accelerating factor. We believe that both anoxemia of the heart muscle due to the coronary sclerosis and/or hypertension are important. We must disagree with Kleinfeld and Redish[39] who imply that enlargement of the heart is neither related to coronary sclerosis or to hypertension.

Enlargement of the heart was more frequent in women than in men with coronary occlusion and occurred at a later age. Since the incidence of hypertension in this disease is so much greater in women than in men, almost 3 to 1, it is evident that high blood pressure is important for the enlargement of the heart in women, at least. Nevertheless, even in this sex, large hearts were observed in the absence of high blood pressure. This is not the place to discuss in detail the reasons for the much greater incidence of hypertension in women than in men with

coronary artery occlusion.   The problem is still unsolved, although fascinating.[40]
Men experience coronary occlusion so much more frequently than women, they
suffer it at an earlier age, and nearly three-fourths of the men possess normal
blood pressure, whereas nearly three-fourths of the women have hypertension
prior to the coronary accident.   Lipid protein metabolism and sex hormones may
be factors not only in the pathogenesis of coronary occlusion but also in the
genesis of hypertension and enlargement of the heart in this disease.[40]

<div align="center">CONCLUSIONS</div>

Enlargement of the heart, in cases of coronary occlusion, has hitherto been
generally attributed to hypertension.   This opinion was based on erroneous
definitions of hypertension, since the variations of pressure in different age groups
and in the sexes were not taken into account.   We have, therefore, reconsidered
the causation of cardiac enlargement in such cases, using the newly established
limits of hypertension.

Of the 500 men who suffered coronary occlusion, 136 had had hypertension,
332 had had normal pressure, and thirty-two were borderline cases.   Seventy-
seven of the 500 (15.4 per cent) had definitely enlarged hearts.   Of these seventy-
seven, twenty-nine had hypertension, forty-five had normal blood pressure, and
three were borderline cases.   The frequency of cardiac enlargement in those with
hypertension was 21.3 per cent and in those with normal blood pressure it was
13.6 per cent.

At least twenty-seven of the patients with normal pressure and large hearts
had never been in heart failure.   Heart failure, therefore, is not an essential
factor in the production of cardiac enlargement in those with normal blood
pressure.

Hypertension does not predispose to ventricular aneurysm any more than
does normal blood pressure.

Cardiac enlargement was more frequent in the hypertensive patients in each
age group.   It seems clear, then, that hypertension is a factor in the causation of
enlargement of the heart, in those who suffer from coronary occlusion.

The incidence of enlargement of the heart increased sharply at the age of 55
in patients with normal blood pressure.   Age, with its associated coronary
sclerosis is also an important cause of cardiac enlargement in coronary occlusion.
When both hypertension and coronary sclerosis (the aging process) occur simul-
taneously, the incidence of cardiac enlargement is most frequent—almost two-
fifths of the cases of coronary occlusion.

Among the 100 women studied, forty-four had enlargement of the heart.
The ratio of cardiac enlargement among the women was almost three times that
among the men—44.0 per cent to 15.4 per cent.   This higher frequency was found
among the hypertensive group—women 52.2 per cent and men 21.3 per cent, as
well as among those with normal blood pressure—women 23.8 per cent and men
13.6 per cent.

Hypertension occurred in 71 per cent of the female patients and in 27 per
cent of the male patients.   Since 71 per cent of the women with coronary occlusion

had hypertension, and since 44 per cent had cardiac enlargement, hypertension appears to be an important cause of enlargement of the heart in women.

In women with coronary occlusion the frequency of cardiac enlargement was greatest in the 60 to 64 year age group when coronary sclerosis and hypertension both occurred most often.

Since 21 per cent of the women had a normal blood pressure, and since 23.8 per cent of these had an enlargement of the heart, coronary sclerosis alone also appears to be a cause of cardiac enlargement.

The combination of hypertension and coronary sclerosis (the aging process) is the most important factor in the causation of enlargement of the heart in patients who suffer from coronary occlusion.

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STUDIES OF PULMONARY HYPERTENSION. IV.

PULMONARY CIRCULATORY DYNAMICS IN PATIENTS WITH MITRAL STENOSIS AT REST

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DURING the past 3 years physiologic studies of patients with mitral stenosis have been reported from various laboratories.[1-17] Most of these patients tend to have decreased cardiac output, elevated pulmonary "capillary" and pulmonary artery pressures, and increased pulmonary resistance. Many show increased work of the right ventricle against pressure and physiologic evidence of right ventricular failure. Pulmonary hypertension correlates well with the degree of disability.

It is the purpose of this paper (a) to present physiologic data of forty-three patients with predominant mitral stenosis, (b) to correlate various determinants related to pressure and flow in the pulmonary circuit, and (c) to emphasize the importance of pulmonary "capillary" pressure and its relation to other factors.

CLINICAL MATERIAL AND METHOD

Forty-three patients with predominant mitral stenosis and minimal degrees of other valvular involvement were studied. There were sixteen men and twenty-seven women, ranging in age from twelve to forty-nine years. They were classified clinically according to the criteria recommended by the New York Heart Association. There were two patients in Group 1, nine in Group 2, twenty-one in Group 3, and eleven in Group 4.

A rumbling mid-diastolic or a late diastolic murmur was heard at the apex in all cases. In twenty-two patients an apical systolic murmur of Grade 1 or Grade 2 intensity was present. In fifteen patients there was a blowing diastolic murmur

along the left sternal border.   This murmur was interpreted as the Graham Steell murmur of pulmonary insufficiency in thirteen cases, and as that of mild aortic insufficiency in the remaining two cases (A. Ge., C. A.).   One patient (J. C.) had tricuspid incompetence.   Two patients (G. R., and H. G.) had associated essential hypertension.   Fifteen patients had a few râles at the base of both lungs. Thirty-four patients were receiving maintenance dosages of a digitalis preparation. One or more 12-lead electrocardiograms were made on each patient.   Twenty-six patients had sinus rhythm, and seventeen had atrial fibrillation at the time of study.   Abnormal P waves were demonstrated in ten patients and evidence of right ventricular hypertrophy in twenty.   Fluoroscopy and roentgenograms of the chest showed unequivocal enlargement of the left atrium in forty patients, slight or doubtful enlargement in two, and no enlargement in the remaining one. Definite dilatation of the pulmonary artery was demonstrated in all but one.

Cardiac catheterization was performed on each patient two or three hours after a light breakfast, according to a modification of the method of Cournand and Ranges.[18]   With few exceptions no premedication was administered.   Pulmonary "capillary" pressure was recorded by the method of Hellems and associates.[19]

A No. 19-needle was inserted into the brachial or femoral artery and connected to a pressure drip of aqueous 5 per cent dextrose.   When ventilation was stable, cardiac output was determined by the direct Fick principle.   Oxygen consumption was measured by a method similar to that described previously.[20] Blood samples were withdrawn simultaneously from systemic and pulmonary arteries as oxygen consumption was determined.   Blood oxygen content, capacity, and saturation were analyzed by the method of Van Slyke and Neill.[21] Pressures were recorded in pulmonary and systemic arteries after measuring cardiac output.   Finally, the catheter was withdrawn to the right ventricle, right atrium, and superior vena cava.   Pressure records were obtained from each site.

Pressures were recorded by means of a Statham strain gauge connected to a carrier wave-amplifier in a multi-channel direct-writing oscillograph (Sanborn Poly-Viso Cardiette).   The electrocardiogram and pneumogram were recorded simultaneously.   Pressure records were calibrated with a mercury manometer. Systolic and diastolic pressures were measured for at least two respiratory cycles, and average values calculated.   Mean pressures were measured by planimetric integration of pressure tracings during at least two respiratory cycles.   The arbitrary zero point of all pressures was 6.5 cm. below the angle of Louis with the patient recumbent.

Peripheral and pulmonary resistances and ventricular work against pressure were calculated by the formulas described by Gorlin and associates.[4]   Mitral valve areas were calculated by the formula of Gorlin and Gorlin,[22] and that of Ravin and associates,[12] respectively.   The latter formula is limited by its assumption of fixed "pulmonary capillary" pressure.   Pulmonary "capillary" pressure (PC_m) agreed well with pulmonary artery diastolic pressure (PA_d) in most cases.   Therefore, pulmonary artery diastolic pressure was substituted for pulmonary "capil-

lary" pressure, and mitral valve area was calculated using the formula of Gorlin and Gorlin.[22] The limitations of this substitution will be discussed in a subsequent section.

<div align="center">OBSERVATIONS</div>

The pertinent data are presented in Table I with patients listed in order of increasing pulmonary artery mean pressure.

1. Pulmonary Artery and "Capillary" Pressures and Gradient.—Pulmonary artery and "capillary" pressures were elevated in all patients with the exception of G. R. The highest pulmonary artery mean pressure was 86 mm. Hg, and the highest pulmonary "capillary" pressure was 39 mm. Hg. In general, the magnitude of pulmonary artery pressure varied directly with pulmonary resistances, arteriovenous oxygen difference, right ventricular work, and inversely with mitral valve area. With two exceptions all patients whose pulmonary artery mean pressure exceeded 30 mm. Hg had a calculated mitral valve area of less than 1.0 cm.[2] Pulmonary "capillary" pressure correlated positively with pulmonary artery mean pressure and total pulmonary resistance, but not with pulmonary arteriolar resistance. Cardiac index correlated with pulmonary artery mean pressure ($r = 0.319$, $N = 43$) with significance at the 5 per cent level. It is noteworthy that the patients with higher pulmonary artery and "capillary" pressure were more disabled than those with low pressures.

A significant correlation was found between pulmonary "capillary" pressure and pulmonary artery diastolic pressure ($r = 0.825$, $N = 32$). The correspondence was more evident when pulmonary "capillary" pressure did not exceed 30 mm. Hg. Beyond this limit there was usually a precipitous increase, absolute and relative, in pulmonary artery diastolic pressure. Similar observations have been made by other investigators.[2,4,13]

The mean pulmonary artery-pulmonary "capillary" pressure gradient was variable. It was 10 mm. Hg or less (upper limit of normal) in ten patients. In general, the more disabled the patient, the higher the gradient. The mean pulmonary artery-pulmonary "capillary" pressure gradient was 12 mm. Hg or less with pulmonary artery mean pressures below 47 mm. Hg, except in one patient. With higher pulmonary artery mean pressure, the gradient was 14 mm. Hg or higher in all patients except one.

2. Pulmonary Resistance.—Total pulmonary resistance was higher than normal in all but one patient. There was considerable variation in pulmonary arteriolar resistance, although it was elevated in twenty-four out of the thirty-two patients in whom pulmonary "capillary" pressure was measured. Total pulmonary resistance and pulmonary arteriolar resistance varied directly with pulmonary artery mean pressure and arteriovenous oxygen difference, and inversely with mitral valve area, cardiac index, stroke index, and left ventricular work. In general, pulmonary resistances increased progressively in patients from Group 1 to Group 4.

3. Cardiac Index.—Cardiac index was slightly elevated in two patients, normal in thirteen and definitely reduced in the remaining twenty-eight patients. Eighteen out of twenty-three patients with a calculated mitral valve area of

1.0 cm.[2] or less had a subnormal cardiac index. In most instances, owing to tachycardia, stroke index tended to be low. In thirty-one out of forty-three patients stroke index was less than 34 c.c./beat/M.[2], the lower limit of normal. All but one patient of Group 4, and the majority of Group 3 had subnormal cardiac and stroke indices. The low cardiac index was manifested by an increased arteriovenous oxygen difference. Oxygen consumption in the majority was within the normal range. The lowest cardiac index occurred in patients V. J. and A. M. whose calculated mitral valve area was 0.4 cm.[2] and whose pulmonary "capillary" pressures were 21 and 38 mm. Hg, respectively. In twenty-two patients right ventricular failure, reflected by elevated right ventricular end-diastolic and right atrial mean pressures, contributed at least partly to the low cardiac index. In general, the cardiac index of patients with atrial fibrillation was slightly lower than that of patients with sinus rhythm at approximately the same ventricular rate. This agrees with the observations of other investigators.[4,16] Cardiac and stroke indices both varied directly with calculated mitral valve area.

4. *Mitral Valve Area.*—The smaller the calculated mitral valve area, the more limited the patient's functional capacity. Many investigators agree that the patient with a calculated mitral valve area of less than 1.0 cm.[2] usually has symptoms related to his disease.[9,10]

In many patients mitral valve area calculated by the formulas of Gorlin and Gorlin, and of Ravin and associates gave results within 0.2 cm.[2], but in several patients (A. B., R. F., R. S., E. K.) striking discrepancy was noted. Mathematically, the formula of Ravin and associates[12] yields larger values than that of Gorlin and Gorlin[22] for calculated mitral valve area when cardiac output is normal; the converse applies when pulmonary "capillary" pressure is normal or only slightly increased.

The mitral valve area of patient G. R. was not calculated because the pulmonary "capillary" pressure was normal. The physical signs of mitral stenosis in this case were unequivocal. Although she had symptoms including exertional dyspnea she was classified under Group 1, inasmuch as her symptoms apparently were unrelated to mitral stenosis. During cardiac catheterization she was relaxed and calm, and her oxygen consumption was normal. The increased cardiac output, manifested by narrow arteriovenous oxygen difference, could not be satisfactorily explained.

· Technical difficulty in wedging the catheter tip in the distal pulmonary artery, which we encountered in certain patients, prompted us to assess the reliability of substituting pulmonary artery diastolic pressure for pulmonary "capillary" pressure in the formula of Gorlin and Gorlin[22] for mitral valve area. When pulmonary artery diastolic pressure was 30 mm. Hg or less, the pulmonary "capillary" pressure differed from it by 4 mm. Hg or less in thirteen of fifteen patients, the algebraic mean difference being zero. When pulmonary artery diastolic pressure was more than 30 mm. Hg, it exceeded pulmonary "capillary" pressure by 5 mm. Hg or more in fifteen of seventeen patients, with an average difference of 8 mm. Hg and a range of 3 mm. to 24 mm. Hg. In spite of this, the three instances in which the two calculations yielded values for mitral valve

TABLE I. SUMMARY OF THE CLINICAL AND PHYSIOLOGIC DATA IN 43 PATIENTS WITH MITRAL STENOSIS

CASE	BSA (M²)	CLINICAL CLASSIFICATION	CARDIAC OUTPUT DETERMINATION AND BLOOD GAS ANALYSIS					PRESSURES (MM. HG)							RESISTANCES (DYNES/SEC./CM.⁵)			MITRAL VALVE AREA (CM²)			VENTRICULAR WORK AGAINST PRESSURE (KG.M/MIN./M²)	
			OXYGEN CONSUMPTION C.C./MIN./M²	A-V OXYGEN DIFFERENCE VOL. (%)	CARDIAC INDEX L/MIN./M²	STROKE INDEX C.C./BEAT/M²	OXYGEN SATURATION %	SYSTEMIC ARTERY S/D	SYSTEMIC ARTERY MEAN	PULMONARY ARTERY S/D	PULMONARY ARTERY MEAN	"PULMONARY CAPILLARY" MEAN	RIGHT VENTRICLE D	RIGHT ATRIUM MEAN	TOTAL PERIPHERAL	TOTAL PULMONARY	PULMONARY ARTERIOLAR	GORLIN AND GORLIN (USING PC)	GORLIN AND GORLIN (USING PA)	RAVIN ET AL.	LEFT	RIGHT
G. R.	1.61	I	134	2.46	5.5	74	94	160/95	125	24/9	15	7	4	3	1138	137	73				9.4	2.6
S. M.	1.60	II	113	4.00	2.9	38	93	88/64	75	27/15	18	14		2	1301	315	65	1.3	1.2	1.1	2.9	0.7
A. B.	1.47	I	173	7.00	2.5	30	95	104/75	88	41/17	24	13	4	2	1940	525	239	1.2	0.8	0.8	2.9	0.8
J. J.	1.48	II	136	2.68	5.1	71	85	100/49	69	34/17	25	19	2	1	734	266	64	1.5	1.6	2.1	4.7	1.8
H. C.	2.00	II	124	3.37	3.7	45	94	126/78	95	40/20	26	17	3	2	1025	282	97	1.9	1.2	2.1	4.7	1.3
R. F.	1.72	II	110	3.31	3.3	48	93	144/77	103	40/20	28	22	7	7	1441	350	84	1.4	1.4	1.5	4.7	1.0
M. B.	1.81	III	130	4.39	3.0	31	88	90/47	64	52/17	28	24	2		860	422	180	0.9	0.9	0.9	2.5	1.3
L. B.	1.69	III	163	6.60	2.5	29	91	114/70	86	43/24	31	22	7	9	1640	590	171	0.8	0.8	0.9	2.9	0.8
P. P.	1.55	III	132	5.09	2.6	40	96	100/54	67	39/22	33	26	8	6	1380	680	140	1.0	1.1	1.3	2.2	1.0
F. M.	1.81	II	104	3.85	2.7	38	88	78/62	69	48/22	35	25	4	1	1110	572		0.5	0.5	0.4	2.5	1.3
J. C.	1.54	IV	94	5.62	1.7	24	95	94/59	73	60/29	38	27	18	16	2240	1160	340	0.5	0.5	0.8	1.3	0.5
E. A.	1.91	II	141	7.58	1.9	22	92	106/72	83	59/26	41	29	8	14	1900	940	268	0.5	0.8	0.9	2.1	0.7
P. D.	1.77	III	127	5.56	2.3	22	96	114/56	82	52/32	41	21	4	2	1650	825	404	1.1	0.9	1.3	2.5	1.3
R. S.	1.67	III	128	4.20	3.1	36	91	123/80	91	59/34	41	29	10	6	1422	722	185	0.9	0.9		3.8	1.5
P. vE.	1.80	III	146	8.64	1.7	25	97	120/90**		60/29	41		5	3		1067						0.9

C. A.	1 42	III	112	4.38	2.6	28	92	118/60	82	61/30	42	35	2	1	1843	940	150	0.5	0.6	0.8	2.8	1.5
A. Ge.	1 72	IV	154	7.50	2.1	25	95	150/70**	—	77/30	44	—	10	14	—	1010	805	0.7	0.5	—	—	0.9
A. L.	1 88	III	140	6.67	2.1	35	90	137/83	111	67/33	47	23	7	9	2280	1270	1150	0.4	0.3	0.9	3.1	1.2
V. J.	1 36	III	115	8.52	1.3	11	94	136/86	100	66/37	47	21	6	7	4460	2805	—	0.4	0.3	0.2	1.8	1.1
J. M.	1 96	III	133	9.01	1.5	28	94	126/87	103	69/31	48	—	7	9	2820	1320	327	—	—	—	5.4	0.8
M. N.	1 57	IV	130	4.85	2.7	28	88	148/93	117	68/37	49	32	6	8	2230	948	678	0.7	0.7	1.0	4.3	1.6
L. C.	1 42	IV	130	6.90	1.9	26	92	155/75	92	80/38	49	30	12	9	2712	1562	—	0.4	0.3	0.5	2.4	1.2
J. O.	1 47	IV	121	7.40	1.7	17	82	110/80**	—	64/45	50	—	8	10	—	1568	—	—	—	—	—	0.9
A. Ga.	1 53	IV	168	7.97	2.1	17	89	96/54	66	75/38	50	30	3	1	1670	1260	537	0.6	0.5	0.6	1.8	1.5
G. T.	1 60	IV	85	5.80	1.5	15	87	128/82	89	57/44	51	36	6	6	3000	1696	499	0.4	0.3	0.4	1.8	0.9
D. P.	1 57	II	135	4.89	2.8	29	96	95/60	71	66/39	51	—	9	7	1354	730	258	—	—	—	2.7	2.3
J. B.	1 69	III	155	4.31	3.6	35	85	138/74	96	70/36	53	31	−1	1	1240	658	134	1.1	1.0	1.7	4.7	2.7
L. F.	1 56	II	134	3.06	4.4	49	87	84/49	63	71/42	53	39	2	2	743	624	—	1.0	1.0	1.9	3.6	3.3
M. S.	1 68	III	143	6.94	2.1	19	89	125/74	94	74/30	53	—	10	10	2050	1200	482	—	—	—	2.6	1.4
E. C.	1 71	IV	129	5.91	2.2	14	94	95/72	79	76/41	54	32	4	7	1790	1200	582	0.8	0.7	0.8	2.3	1.5
F. L.	1 50	III	135	4.09	2.2	22	87	157/86	118	76/30	54	30	4	5	2490	1308	714	0.6	0.7	0.7	3.5	1.3
C. S.	1 65	III	146	7.54	1.9	26	93	79/54	57	83/30	55	25	5	4	1415	1330	325	0.5	0.5	0.7	1.5	1.4
A. C.	1 55	III	127	6.00	2.1	29	88	142/83	98	76/44	56	39	12	9	2340	1300	438	0.9	0.8	0.5	2.8	1.4
R. R.	1 37	III	151	4.88	3.1	32	89	130/73	90	83/36	56	31	3	1	1220	982	520	0.4	0.3	1.1	3.8	2.5
A. M.	1 67	IV	107	7.89	1.3	10	82	121/72	80	85/46	58	38	20	17	3030	1720	375	0.7	0.7	0.3	1.3	1.0
L. R.	1 69	IV	145	4.77	3.0	34	75	148/75	97	90/37	58	34	3	7	1510	910	476	0.9	0.8	1.3	4.0	2.1
E. K.	1 64	III	166	4.62	3.6	44	86	153/81	117	114/45	71	36	13	8	1590	964	—	—	—	1.6	5.8	3.5
H. G.	1 82	III	185	6.60	2.8	28	90	192/118	148	115/36	73	—	12	12	3865	858	—	—	—	—	5.8	2.5
M. R.	1 47	III	197	4.96	4.0	34	84	145/83	96	120/45	73	—	0	1	1410	1071	—	—	—	—	3.8	4.1
H. D.	1 39	IV	155	8.49	1.8	18	86	120/90	100	117/50	74	—	13	17	3060	2270	1443	0.4	0.3	—	2.5	1.8
B. R.	1 11	IV	151	7.33	2.1	19	—	105/80**	—	97/58	75	34	7	5	—	2641	—	—	—	0.3	—	2.1
S. N.	1 88	IV	142	7.10*	2.0	25	85	102/63	77	122/61	80	—	17	22	1714	1776	—	—	—	—	1.7	1.4
M. H.	1 65	III	170	8.90*	1.8	17	90*	104/87**	—	134/54	86	—	8	9	—	2288	—	—	—	—	—	2.0

*Arterial samples obtained 24 hours after catheterization, under similar conditions.

**Blood pressure measured by sphygmomanometry.

area differing by 0.2 cm.^{2} or more appeared in patients with relatively low diastolic pressures (17, 32, and 33 mm. Hg, respectively). In other words, as higher pulmonary artery diastolic pressures were encountered, the higher gradients between pulmonary artery diastolic and pulmonary "capillary" mean pressures were not reflected in increased discrepancy between mitral valve areas calculated by Gorlin and Gorlin's formula with and without substitution of pulmonary artery diastolic for pulmonary "capillary" mean pressure. Our data are insufficient, however, to warrant conclusions on the validity of the substitution when pulmonary artery mean pressure is above 60 mm. Hg.

5. *Ventricular Work Against Pressure.*—(a) Left ventricular work. Except for patient G. R., all patients showed either normal or reduced left ventricular work. Calculated mitral valve area varied directly with left ventricular work. This is not surprising since, as the mitral valve orifice becomes smaller, blood flow through the valve is reduced and hence left ventricular work is decreased. This also explains the absence of left ventricular hypertrophy in pure mitral stenosis.

(b) Right ventricular work. In twenty-seven patients the right ventricular work was greater than the upper limit of normal (1.2 kg.M/min./M.^{2}). It was high in patients of Group 3 and lower in patients of Group 4, presumably because of right ventricular failure. The high right ventricular work in patient G. R. was manifested by a comparatively large cardiac output.

6. *Arterial Blood Oxygen Saturation.*—The oxygen saturation of arterial blood was below 94 per cent in thirty patients, the lowest figure being 75 per cent. In general, the more disabled the patient the lower the arterial blood oxygen saturation. In seven out of eleven patients of Group 4 the arterial oxygen saturation was below 90 per cent.

DISCUSSION

The important physiologic changes in most patients with mitral stenosis are (a) increase in pressures and resistances in the pulmonary circuit, and (b) decrease in cardiac index and stroke index. These have been discussed by many investigators.[4,6,7,11,13]

In human subjects there is at present no practical method of recording pressures in either the pulmonary vein or left atrium in the absence of septal defect except at operation. The method of recording pulmonary "capillary" pressure described by Hellems and associates[19] provides valuable information in the physiologic study and understanding of cardiopulmonary disease. Dow and Gorlin[23] and Calazel and associates[24] have shown that pulmonary "capillary" pressure may be regarded as a crude index of pulmonary venous and left atrial pressures. Recent studies by Connolly and associates[25] showed that there was a close agreement between left atrial pressure and pulmonary artery wedge pressure (pulmonary "capillary" pressure) obtained simultaneously at operation. Since, in most patients with mitral stenosis, left atrial pressure rises in maintaining an adequate blood flow through the stenotic mitral valve, a similar rise in pulmonary "capillary" and pulmonary artery pressures may be expected.

Pulmonary "capillary" pressure is of practical importance in differentiating precapillary from postcapillary pulmonary hypertension.[26] In precapillary pulmonary hypertension, represented by patients with chronic pulmonary disease, pulmonary "capillary" pressure at rest is usually normal. On the other hand, in postcapillary pulmonary hypertension, occurring in mitral stenosis, pulmonary "capillary" pressure is almost always elevated. In chronic pulmonary disease pulmonary "capillary" pressure does not correlate significantly with pulmonary artery diastolic and mean pressures,[26] whereas in mild and moderate mitral stenosis an excellent correlation is observed. However, no significant correlation exists between pulmonary "capillary" pressure and pulmonary arteriolar resistances in either group. The response of pulmonary "capillary" pressure to various stresses is also dissimilar and will be described in detail in a subsequent communication.[27]

This differentiation is important because it emphasizes that the mechanism underlying the pulmonary hypertension is not the same. In chronic pulmonary disease, pulmonary hypertension is presumably due to the effects of one or more of the following factors:[26,28-34] (a) anatomic changes in small pulmonary vessels, (b) anoxia, (c) hypervolemia, and (d) hypercapnia. Normal pulmonary "capillary" pressure indicates that the left side of the heart is not involved.

In mitral stenosis pulmonary hypertension in the initial stage is principally due to elevated left atrial, pulmonary venous, and pulmonary "capillary" pressures. The pulmonary artery-pulmonary "capillary" pressure gradient is usually maintained below 15 mm. Hg. This has been designated passive pulmonary hypertension by Baker and associates.[11] In many cases when pulmonary "capillary" pressure exceeds 30 mm. Hg, pulmonary artery mean pressure is disproportionately high and the pulmonary artery-pulmonary "capillary" pressure gradient is well beyond the limits of passive pulmonary hypertension (Fig. 1). Assuming little change in the already reduced cardiac output, the higher gradient implies an actual increase in pulmonary arteriolar resistance proximal to the capillary bed. This increase in pulmonary arteriolar resistance may be caused by (a) irreversible pathologic changes in the pulmonary vascular tree in long-standing mitral stenosis,[35-37] or (b) reversible physiologic disturbance such as pulmonary arteriolar vasoconstriction,[4,32] or both.

According to Poiseuille's law, blood flow per unit time is directly proportional to the pressure gradient and inversely proportional to resistance. In the pulmonary circulation this principle applies where blood flow is represented by cardiac output, pressure gradient by the mean pulmonary artery-pulmonary "capillary" pressure gradient, and resistance by pulmonary arteriolar resistance.

In a hypothetical case of mitral stenosis pulmonary "capillary" pressure may rise from a normal level of 10 mm. Hg to 25 mm. Hg without actually producing pulmonary edema. If no change in blood flow or pulmonary arteriolar resistance occurs, mean pressure in the pulmonary artery will rise to the same extent as that of the pulmonary "capillary." If pulmonary arteriolar resistance increases but blood flow remains constant, this increased resistance cannot affect pulmonary "capillary" pressure. On the other hand, with an increase in blood flow pulmonary "capillary" pressure will rise regardless of change in pulmonary arteriolar

resistance. The only mechanism by which pulmonary "capillary" pressure can be reduced is (a) decrease in pulmonary blood flow, or (b) relief of obstruction at the mitral valve. Therefore, pulmonary arteriolar resistance can only prevent a rise in pulmonary "capillary" pressure to the extent that it may prevent an increase in pulmonary blood flow.
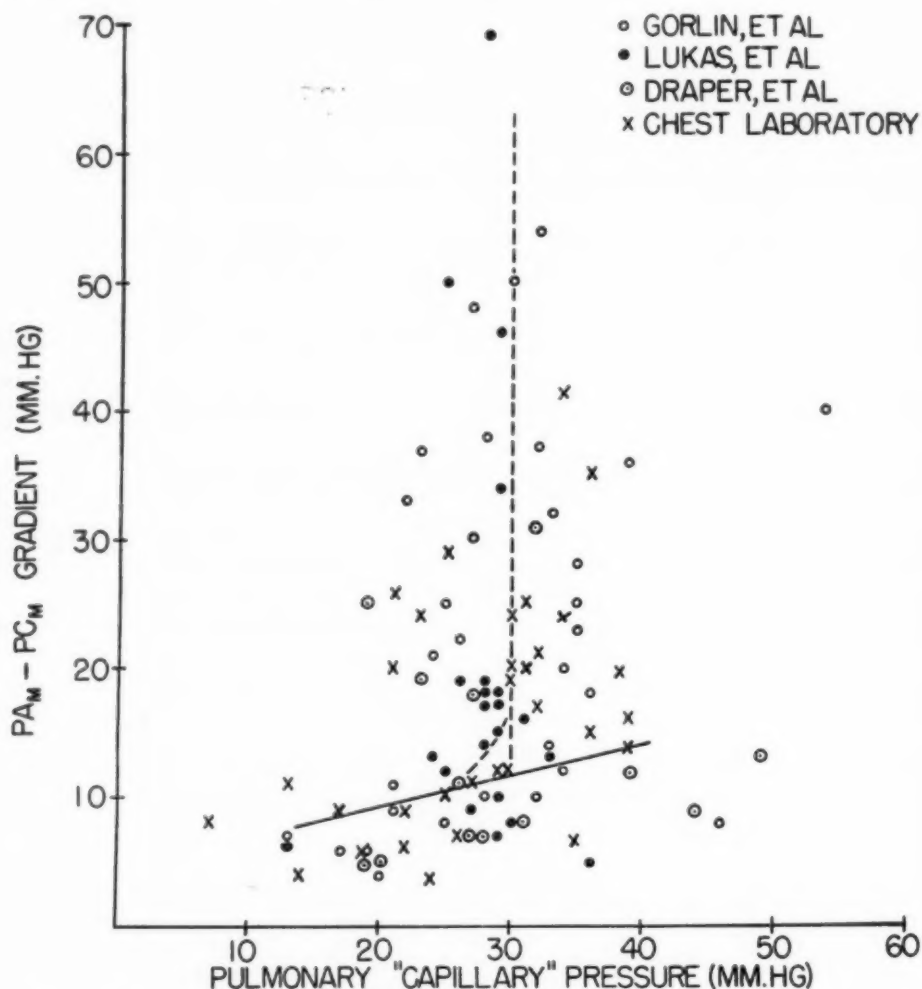

Fig. 1.—This graph shows pulmonary "capillary" pressure plotted against mean pulmonary artery-pulmonary "capillary" pressure gradient in patients with mitral stenosis studied in different laboratories including our own. The arbitrary solid line indicates a parallel rise in pulmonary "capillary" and artery mean pressures up to the hypothetical edema level (30 mm. Hg). Beyond this point, in a large number of cases, pulmonary artery mean pressure rises sharply with little change in pulmonary "capillary" pressure. Hence the gradient tends to widen considerably, as indicated by the arbitrary dotted line.

Dexter and associates[2,4,5,8] have suggested that increased pulmonary arteriolar resistance may protect the pulmonary "capillary" bed from the sudden surge of blood from a competent right ventricle, thus preventing the development of pulmonary edema. However, this concept has been recently challenged by

Araujo and Lukas,[14] who postulate possible regulation of cardiac output by re-
flexes originating from pressure receptors in the left atrium or the pulmonary
veins.   Inasmuch as heart rate is not slowed, the mechanism by which such
hypothetical reflexes reduce cardiac output is unknown.   If, as suggested by
Araujo and Lukas, increased pulmonary arteriolar resistance is primarily caused
by irreversible structural changes, one would not expect a significant reduction
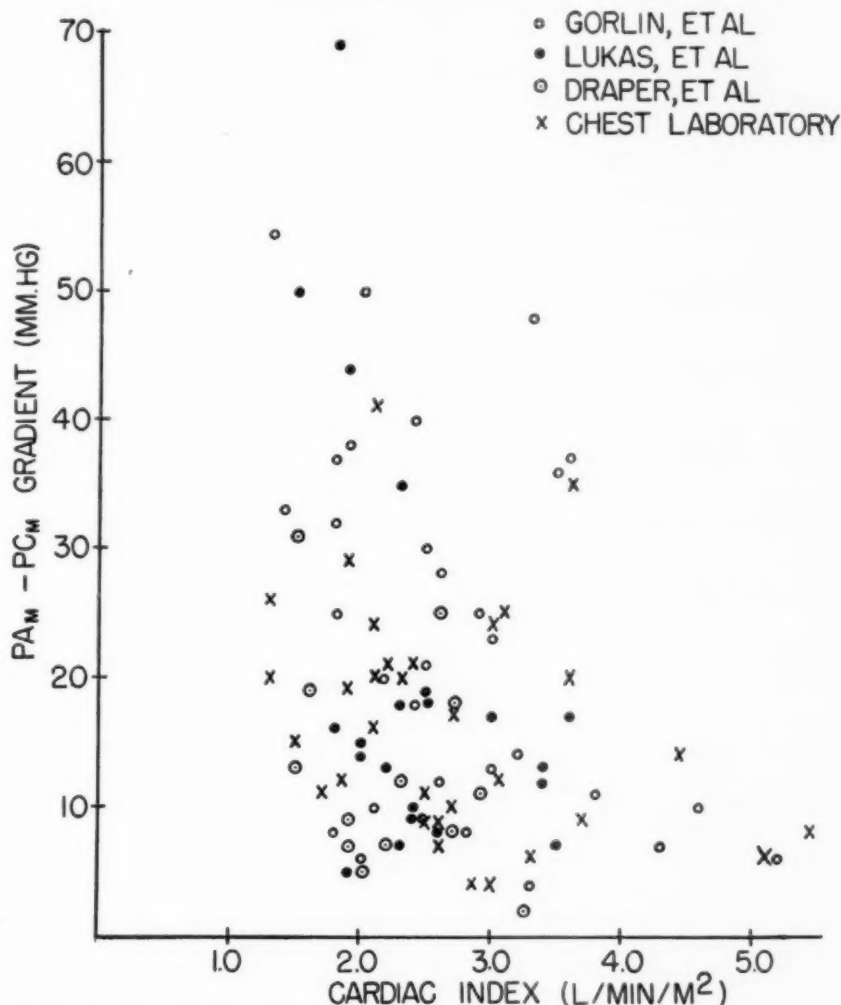

Fig. 2.—Cardiac index is plotted against mean pulmonary artery-pulmonary "capillary" pressure
gradient in patients with mitral stenosis studied in different laboratories including our own.   There is
a negative curvilinear relationship between these two determinants in most cases.   The negative co-
efficient of correlation (r = — 0.325; P < 0.01) is highly significant.

in pulmonary arteriolar resistance after mitral valve surgery.   However, the
pronounced reduction in pulmonary arteriolar resistance in many patients after
mitral valve surgery[9,38,39] shows that increased pulmonary arteriolar resistance is
at least partly reversible.   Furthermore, if cardiac output is reduced solely by

reflex mechanisms, according to Poiseuille's law, pulmonary artery pressure and pulmonary artery-pulmonary "capillary" pressure gradient would be expected to fall.   In most cases, however, reduced cardiac output is associated with increased pulmonary artery pressure and pulmonary artery-pulmonary "capillary" pressure gradient (Fig. 2).   These considerations suggest that increased pulmonary arteriolar resistance plays a significant role in regulating the cardiac output of many patients with mitral stenosis under static conditions.

However, during excitement, exercise, or tachycardia, the situation may be quite different.   Gorlin and associates,[4] and Lukas and co-workers[13,14] showed that most patients with mitral stenosis manifest little or no increase in pulmonary arteriolar resistance after exercise, although there is usually a parallel rise in cardiac output and pulmonary "capillary" pressure.   The consequent increase of pulmonary blood flow elevates both pulmonary artery and "capillary" pressures, readily provoking pulmonary edema.

About one-third of the patients in this series had râles at the lung bases before cardiac catheterization, and two of them (P. D. and G. T.) developed frank pulmonary edema during the procedure.   The pulmonary "capillary" pressures measured during the attacks were 38 and 36 mm. Hg, respectively.   The tip of the catheter had been wedged in a distal radicle of the pulmonary artery for more than 15 minutes, and undue tachycardia was present in each case.   In patient P. D. the initial pulmonary "capillary" pressure was only 21 mm. Hg, and as the pressure rose to 38 mm. Hg pulmonary edema developed.   No evidence of pulmonary edema occurred in an additional four patients (A. C., E. K., A. M. and L. F.) who had pulmonary "capillary" pressures of similar magnitude and in whom the tip of the catheter was in the pulmonary "capillary" for less than 5 minutes.   Gorlin and associates[4] observed pulmonary edema in six out of twenty-one patients with mitral stenosis studied at rest, always associated with either an increased cardiac output, or a shortened diastolic filling period.   On the other hand pulmonary edema was uncommon in the series reported by Lukas and associates.[13,14]   The latter investigators suggested that two factors are uppermost in preventing pulmonary edema.   These are (a) selective fixation of resting pulmonary venous pressure at the level of plasma osmotic pressure by reduction of cardiac output; and (b) decreased permeability of the alveolocapillary membrane.

Thus, the development of pulmonary edema in patients with mitral stenosis during cardiac catheterization appears to depend upon balance of the following factors: (a) duration of "capillary" irritation (a probable reflex mechanism), (b) sudden increase in cardiac output or heart rate,[4,5] (c) degree of alveolar membrane permeability to fluid,[14] and (d) individual variation in plasma osmotic pressure.[14]   Therefore, the tip of the catheter should not be left in the distal pulmonary artery too long, especially when the control pulmonary "capillary" pressure is 25 mm. Hg or higher.   Persistent cough invariably increases pulmonary "capillary" pressure to a high level[39] and may suggest imminent pulmonary edema; the tip of the catheter should be immediately withdrawn to the proximal portion of the pulmonary artery.

SUMMARY AND CONCLUSIONS

1.   Physiologic data at rest are presented on forty-three patients with predominant mitral stenosis.

2.   Hemodynamic observations on these patients are analyzed and the results compared with their functional capacity.   In general, the more severely disabled patients manifested higher pulmonary artery and "capillary" pressures, wider pulmonary artery-pulmonary "capillary" mean pressure gradient, and higher pulmonary resistance.   They had lower cardiac index, stroke index, and arterial blood oxygen saturation.

3.   Correlations between pulmonary artery and "capillary" pressures and some of the determinants have been presented.

4.   Twenty-nine of the thirty-one patients whose pulmonary artery mean pressure exceeded 30 mm. Hg had a calculated mitral valve area of 1.0 cm.^{2} or less.

5.   The value of measuring pulmonary "capillary" pressure is emphasized, particularly in differentiating pulmonary hypertension in mitral stenosis from that in chronic pulmonary disease.   Pulmonary "capillary" pressure was found to correlate with pulmonary artery diastolic and mean pressures, but not with pulmonary arteriolar resistance.   When the pulmonary artery diastolic pressure is less than 30 mm. Hg, it may be substituted for pulmonary "capillary" pressure in the formula of Gorlin and Gorlin in calculating mitral valve area.

6.   Physiologic findings are discussed with particular reference to the mechanism underlying the pulmonary hypertension.

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THE EFFECTS OF CORTISONE AND ACTH ON ARTIFICIALLY INDUCED CARDIAC INFARCTION IN THE DOG*

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IN VIEW of the earlier reported effects of cortisone and ACTH on collagen tissues and wound healing,[1-3] it was decided to observe the effects of these compounds on the healing process of experimentally produced cardiac infarction in the dog. This work was carried out during 1950 to 1951, at which time the available information would tend to suggest that the use of these compounds would have a deleterious effect if used in the presence of cardiac infarction. The possibilities of cardiac rupture during the acute phase and softening of the scarred areas were also considered. On the other hand it was suggested that delayed healing together with inhibition of scar formation might allow for more complete revascularization and the development of collateral channels, thereby possibly reducing the size of the infarct and the effect of occlusion on the myocardial mass in general.

Since the time this work was carried out a number of clinical cases with cardiac infarction have been treated with cortisone and ACTH with no clear-cut or significant effects as far as we know on the cardiac infarct itself. Also, since that time some work has appeared in the literature on the effect of these compounds in experimentally produced cardiac infarction. Johnson and associates[4] have reported that infarct size is markedly reduced in dogs treated with cortisone as compared to control animals. They reported infarcts well over one hundred times larger in the control dogs as compared to the treated group, in addition to a significant decrease in mortality in the treated group. From injection studies these workers also reported an increase in the interarterial coronary anastomosis in the hearts of dogs receiving cortisone and ACTH without ligation of coronary arteries. From their work it would appear that cortisone has an extremely marked effect on both the healing process and infarct size. On the other hand Chapman and associates[5] reported that . . . "Cortisone given in therapeutic amounts to dogs with experimentally produced myocardial infarction produced no deleterious effects on the size of the infarction, or on the rate or quality of myocardial healing."

In view of the divergent results reported in the literature it was felt that our observations although carried out prior to the mentioned work might be of interest. In the experiments to be reported the left circumflex branch of the left coronary artery in the dog was ligated. This branch was used because of our previous experience with ligation of this artery both from the standpoint of mortality and infarct production. Although the mortality is high (in unprotected animals) the infarct size is large, as compared to anterior descending ligation.

In previous work[6] the histological changes occurring following complete coronary occlusion in young healthy dogs were described. In these experiments the effects of anterior descending ligation were studied and by 21 days a firm scar had developed. With circumflex ligation a larger area of infarction is produced, and consequently complete healing may not be observed in many instances by this time and such was found to be the case in the control group of the present investigation. Nevertheless, it was considered from our previous experience that a 21-day period would provide useful and comparable information with regard to infarct healing.

PROCEDURE

In these experiments normal healthy adult dogs were used. In view of the high mortality associated with left circumflex ligation relatively few animals survived for the 21-day period of observation. Ligation of the left circumflex artery was carried out by the method previously described.[6] However, in view of the possible inhibitory effect of cortisone on wound healing the method was modified in that the ligature was tightened and the artery occluded 10 days following operation during which the ligature was placed loosely about the artery. At this time the operative wound was well healed. The animals were placed on a standard dog diet, housed in individual cages, and exercised daily for a short period. The presence of an infarct was confirmed by serial electrocardiograms taken before, during, and following ligation, weights were recorded at frequent intervals, and the animals observed closely for any change in their general condition. They were followed for 21 days after ligation and then sacrificed for pathologic studies.

Three groups of experiments were carried out: Group 1, the effect of cortisone on infarct healing; Group 2, the effect of ACTH on infarct healing; Group 3, the effect of ACTH and cortisone on mortality following sudden ligation of the left circumflex in the conscious dog.

RESULTS

Group 1.—Since the dosage of cortisone had not been established for the dog, the first animal was given 3 mg./kg. per day, administered in a single dose. Attempts to assess the activity of the drug were made by following the eosinophil count, white blood count, and sedimentation rate at frequent intervals. In our hands the eosinophil count was so variable in the dog that little or no useful information could be obtained by this procedure. With the use of 3 mg./kg. per day the first dog became vicious within a few days, then resumed more normal behavior, but by the thirteenth day anorexia and diarrhea were noted with a

one kilogram weight loss.   By the eighteenth day the animal showed shortness of breath, generalized edema, and a purulent nasal discharge despite penicillin therapy.   The animal was obviously ill and died later the same day.   Post-mortem examination revealed a widespread pneumonia and a large soft infarct in the septum and posterior wall of the left ventricle.   On section the wall cut easily and contained cystic areas and blood clots.   Microscopically, there was hemorrhage, necrosis of muscle and loose fibroblastic proliferation.   The infarct was estimated by pathologists as resembling a 7 to 10 day old infarct.   Another animal on the same dosage in which an infarct had not been produced became ill in seven days with signs of pneumonia.   Despite penicillin therapy this animal progressed to a fatal termination on the twentieth day with pleural fistula and convulsions.   Post-mortem examination revealed widespread pneumonia with many adhesions of the lungs to the left chest wall and pericardium.

In view of these effects cortisone in doses of 2 mg./kg. per day was given to the third animal.   On the fourth day following ligation it gradually deteriorated and developed pneumonia by the fourteenth day.   By use of streptomycin the animal survived to the twenty-first day.   Post-mortem examination revealed widespread pneumonia and a large fairly firm infarct which cut with a gritty sensation.   Microscopically the section closely resembled that seen in the animal which died on the 3 mg. dose.   Another animal without an infarct survived the 21-day period on this dosage without untoward effects.   Because of the above experience the dose of cortisone was reduced to $1\frac{1}{2}$ mg./kg. daily and was started 3 days prior to ligation in an attempt to insure an adequate level of the drug at ligation.   Five dogs were carried on this routine for the full 21-day period.   Weight was maintained and the animals appeared well.   The white blood count invariably rose following ligation and gradually settled back to normal levels over a two-week period.   Sedimentation rate showed a slight irregular rise throughout the post-ligation period.   Eosinophil counts were not helpful in assessing the activity of the drug.   The infarcts in these 5 animals varied somewhat in size and averaged 2 to 3 cm. by 3 to 4 cm. and were confined to the posterior wall of the left ventricle and septum.   In the gross they were quite firm and cut with a definite gritty sensation.   Cross section revealed a mottled picture of gray and yellow areas mixed with dark red patches.   Cystic spaces were not a feature. There was no suggestion of cardiac aneurysm or impending rupture.   In these dogs formation of adhesions between the lung and chest wall, along the pericardium, and in the left auriculoventricular recess appeared as extensive as in the control dogs.

Although other controls have been observed in previous work,[6] a series of five control animals was studied at this same time for comparison with these experiments.   In the gross no significant difference was noted between the two groups.   Microscopically the control series showed a moderate amount of loose fibrous tissue, but healing was still not complete in the areas of loosely arranged fibroblastic activity and in other areas disintegration of muscle was still present. In the cortisone dogs it was our impression that dense fibrous tissue was less abundant, but areas of necrosis of muscle and loose fibroblastic activity were somewhat more prevalent.   Occasional clusters of polymorphs were noted and

somewhat more hemorrhage was observed in the cortisone-treated dogs. The sections were examined independently by two experienced pathologists, who had no prior knowledge with regard to the animal from which the section was obtained. No significant difference between the two groups was reported.

Group 2.—Four dogs were followed for a period of 21 days after ligation receiving 3 mg. of ACTH daily administered intramuscularly in 1½ mg. doses at 12-hour intervals. In one of these the drug was started 5 days prior to ligation, but in the remainder it was commenced on the day of ligation. Three of the four ACTH-treated animals developed signs of pneumonia while on this dosage. However, with the assistance of antibiotics the animals survived the post-ligation period of 21 days. Weight loss during the observation period varied between 1 and 3 kilograms, depending on the size of the animal in both the treated and the controlled group. At post mortem the infarcts were again confined to the upper posterior portion of the left ventricular wall and septum and varied in size and thickness. There was no evidence of aneurysm or impending rupture. On section the infarct cut with a gritty sensation and revealed a heterogeneous picture of blood clot, necrotic tissue, and fibrosis. Microscopically, the healing process did not vary significantly from that seen in untreated animals.

Group 3.—From earlier work it is known that the mortality following sudden coronary occlusion in the conscious dog can be significantly reduced, under certain conditions, indicating that the development of fatal ventricular tachycardia and fibrillation can be prevented.[6,7] Since the mechanism by which this fatal event is inhibited is not fully understood and in view of the theoretical possibility of failure of "adaptive mechanism" being responsible[8] a small series of six animals was given ACTH in doses of 3 mg./kg. daily beginning 5 days prior to ligation and 1½ mg. of cortisone daily beginning 3 days before ligation. Five of these six animals died within the first 24 hours, four within 30 minutes of ligation. Although no conclusions can be drawn from such a small series it was apparent that a high mortality rate was occurring with this group quite similar to our previous control studies with ligation of the left circumflex artery in the conscious dog.[6,7]

<div align="center">DISCUSSION</div>

The limited supply of ACTH and cortisone at the time these studies were carried out, and the high mortality associated with left circumflex ligation resulted in the limited number of animals used in this study. Consequently, no statistical comparison can be made, particularly with regard to mortality reported in Group 3. From our present and previous observations, however, it would certainly appear that cortisone and ACTH as used in these experiments would have no significant effect on the immediate mortality following sudden coronary occlusion in the conscious dog. It had been anticipated that cardiac aneurysm and even rupture might follow the use of cortisone in such experiments. This small series suggests, however, that this is unlikely to occur. Although Chapman and associates[5] reported very significant and beneficial effects of cortisone on experimentally produced infarcts the findings from this limited series do not support this view. The microscopic appearance of the sections, when examined

independently by two experienced pathologists, showed no significant effects with regard to infarct healing, although it was our impression that cortisone, particularly in larger doses, may be inhibiting somewhat the healing process.   Further studies with connective tissue stains and collagen assay might have helped confirm or deny this impression.   However, since no significant effect was seen in this limited series of experiments it is our opinion that ACTH and cortisone have little or no effect either on mortality or infarct healing in experimentally produced cardiac infarction in the dog.

SUMMARY

It would appear from this small series that ACTH and cortisone have little or no effect on the healing of experimentally produced cardiac infarction in the dog, and that the use of these substances does not influence in any way the immediate mortality following sudden coronary occlusion in the conscious dog.

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THE EFFECT OF ESTROGENS ON THE PLASMA LIPIDS IN CORONARY ARTERY DISEASE

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THE clinical manifestations of coronary artery disease are uncommon in women before the menopause, whereas in men its consequences are all too frequent even during the fourth decade. This difference between the sexes has led to the suggestion that women may be protected in some way from atherosclerotic processes by a hormonal mechanism.[20] Atherosclerotic plaques contain cholesterol[30] and derive this lipid, at least in part, from the plasma.[3] It has been adequately demonstrated that plasma total cholesterol and the plasma total-cholesterol:phospholipid ratio are both elevated in coronary artery disease.[11,18,21,29] The plasma lipids may be influenced by hormonal secretions, such as thyroxine,[12,17] adrenocorticotrophic hormone,[1,6] cortisone,[1] and insulin.[26] It has been suggested that the plasma lipids undergo cyclical variation in association with the hormonal changes of the menstrual cycle and that depression of plasma total cholesterol at ovulation might be a function of increased endogenous estrogen secretion.[20] Moreover, there is evidence that exogenous estrogens may inhibit the cholesterol-induced atherosclerotic process in the chick[14,22,23] and depress the plasma total-cholesterol:phospholipid ratio in postmenopausal women.[8]

This communication is based on a study of the effect of estrogens on the plasma lipids in a group of men with coronary artery disease.

METHODS

The subjects studied were twenty hypercholesterolemic men, aged 33 to 67 years, with coronary artery disease. The plasma total cholesterol of each subject was greater than 250 mg. per cent before commencing treatment. This criterion for hypercholesterolemia is derived from a previous study of plasma total cholesterol in normal men,[21] the value of 250 mg. per cent being greater than the mean plasma total cholesterol of the normal group plus twice the standard deviation. Plasma-free cholesterol and total cholesterol, hence ester cholesterol by difference, were estimated by the Sperry-Schoenheimer procedure as modified by Sperry and Webb.[27] Plasma lipid phosphorus was estimated by the molybdenum blue method of Allen.[2]

There was electrocardiographic evidence of myocardial ischemia at rest in two of the subjects and of myocardial infarction in eighteen of the subjects. All were outpatients, and therefore blood samples were not taken in the fasting state, but, in order to minimize any postprandial variation, the samples were taken at the same hour of the day at each visit.

The estrogen preparation used in this study was ethinyl estradiol (British Schering); the daily dose was always divided and taken at 8 A.M. and 8 P.M. by all subjects.

1. *Pilot Study.*—A small pilot study was first carried out on three men to determine whether ethinyl estradiol produced any changes in the plasma lipid pattern without undue side effects. After a control period of 7 weeks, these subjects received during the next 10 weeks the following weekly courses of ethinyl estradiol: 0.02 mg., 0.04 mg., 0.06 mg., 0.08 mg., 0.1. mg., 0.1. mg., 0.2. mg., 0.2 mg., 0.4 mg., and 0.4 mg., daily. For reasons to be discussed later 0.2 mg. daily was chosen for the initial dose in subsequent studies. The three men in this preliminary study were excluded from further observations.

2. *Long-Term Study.*—Eleven men, whose plasma lipids had been estimated between 3 and 9 months previously, had further analyses 21 days, 7 days, and 1 day before receiving an initial dose of 0.1 mg. ethinyl estradiol at 12-hour intervals. After two or three weeks the dose was increased to 0.2 mg. every 12 hours, and later to the limit of tolerance as shown by gynecomastia, listlessness, fatigue, and nausea. One man, referred to separately in the text, had to be excluded from this study owing to intolerance. During the period of estrogen treatment seven estimations of the plasma lipids were made at the following intervals: 7, 17, 27, 37, 51, 65, and 79 days. The subjects then received inert tablets for a further 6 weeks, and three estimations were taken at fortnightly intervals. The inert tablets were made to match a tablet of ethinyl estradiol in size and shape and were distributed to the men from an identical unlabelled dark glass bottle. The subjects could not, at any time, have had any suspicion that the pills were different. Clinical notes were made before, during, and after therapy, and are briefly summarized in the text.

3. *Short-Term Study.*—The remaining six men, after three control estimations of their plasma lipids, received 1 mg. ethinyl estradiol a day for 7 days. The plasma lipids were then estimated on the second, fourth, seventh, and fourteenth days after the estrogen course.

RESULTS

From the pilot study it seemed probable that a dose of ethinyl estradiol less than 0.2 mg. daily would not effect a change in the plasma lipid pattern (Fig. 1). The mean plasma total cholesterol remained at about 280 mg. per cent while the subjects received from 0.01 mg. to 0.1 mg. ethinyl estradiol daily; 0.2 mg. daily effected a fall to 257 mg. per cent, and 0.4 mg. daily to 233 mg. per cent. The result of this preliminary study suggested that the possible effective oral dose of ethinyl estradiol would not be less than 0.2 mg. daily.

The mean results of the ten men who received from 0.2 mg. to 0.6 mg. of ethinyl estradiol daily over a period of more than 11 weeks are shown in Figs. 2 and 3. From Fig. 2 it can be seen that considerable depression of the plasma total cholesterol was achieved and this change was confined almost entirely to the ester fraction. The mean plasma total cholesterol, which showed a maximum variation from the mean of 4 per cent during the control period, fell from 314 (±55) mg. per cent immediately before to 236 (±59) mg. per cent at the end of
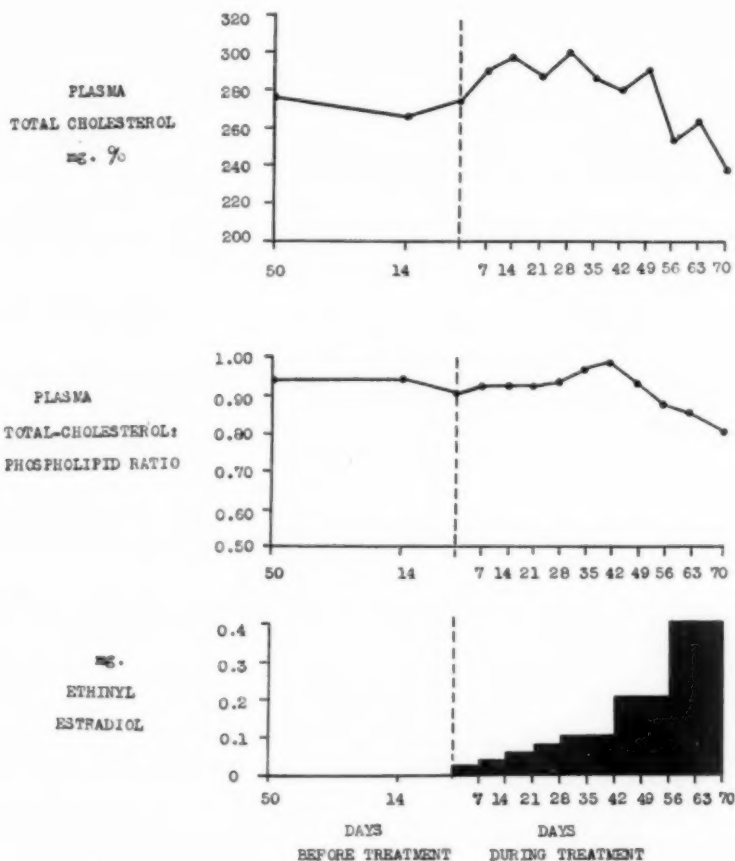

Fig 1.—The pilot study. The effect of increasing doses of ethinyl estradiol on the plasma total cholesterol and the plasma total-cholesterol:phospholipid ratio.

treatment, an average fall of 25 per cent (P <0.01). The plasma total-cholesterol: phospholipid ratio (Fig. 3) was also depressed by virtue of the fall in plasma total cholesterol, the phospholipids remained more or less constant. This ratio, which showed a maximum variation from the mean of 8.5 per cent during the control period, fell from 1.06 (±0.11) immediately before to 0.75 (±0.06) at the end of treatment, an average fall of 29 per cent (P <0.01). Moreover, the mean plasma total cholesterol of the men rose after 6 weeks of inert tablets from 236 mg. per cent to 319 mg. per cent, a rise of 35 per cent; and the plasma total-

cholesterol:phospholipid ratio rose from 0.75 to 1.05, a rise of 40 per cent.   The changes obtained in a typical representative subject are shown in Fig. 4.

Fig. 5 represents the changes in the plasma total cholesterol and the plasma total-cholesterol: phospholipid ratio of the man who twice had to discontinue ethinyl estradiol due to intolerance.   Particular reference to this one subject is of interest because of the repetitive pattern shown by the plasma lipids before and after estrogen therapy.

Fig. 6 represents the alteration in the plasma total cholesterol and the plasma total-cholesterol:phospholipid ratio in six men who received 1 mg. ethinyl estradiol each day for 7 days.
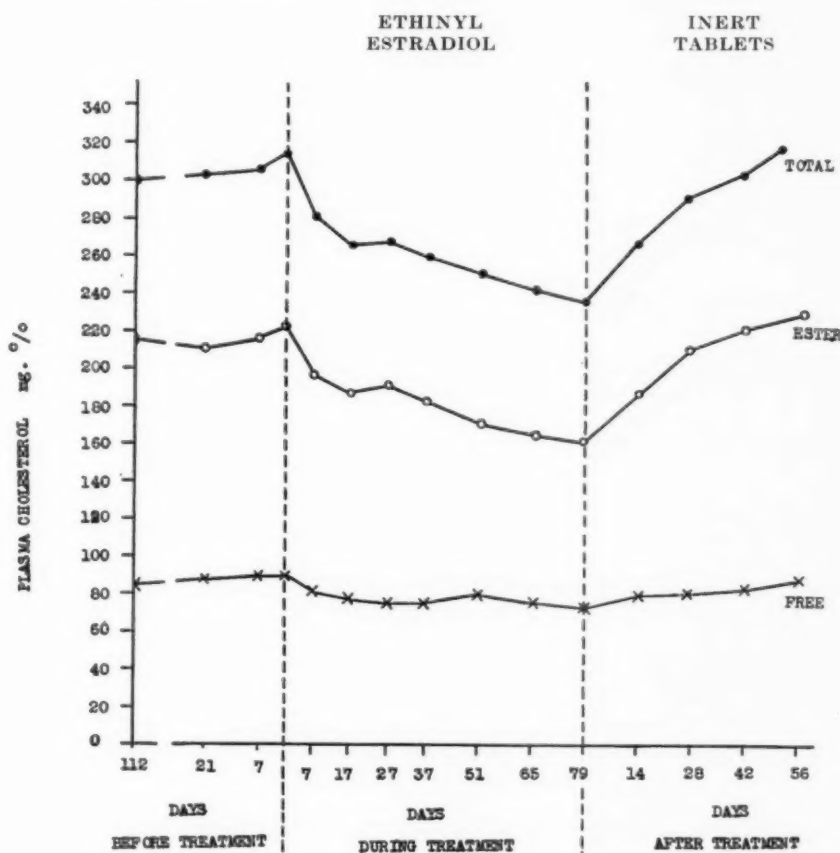

Fig. 2.—Long-term study.   The effect of ethinyl estradiol on the plasma cholesterol fractions.

The distribution of cholesterol between the alpha- and beta-lipoproteins in the plasma of these subjects before, during, and after estrogen therapy will be discussed elsewhere.

The clinical notes of the subjects were of considerable interest particularly those of the twenty who received estrogens for nearly 3 months.   All subjects

were placed before and after estrogen therapy into the grades of functional capacity recommended by the New York Heart Association.[19]   The majority started and finished in Grade 2.   There was no striking change in weight during estrogen or inert tablet administration.

   CASES 1 TO 3.—The pilot study was made up of men aged 38, 55, and 66.   All had electrocardiographic proof of myocardial infarction; all developed mild gynecomastia.
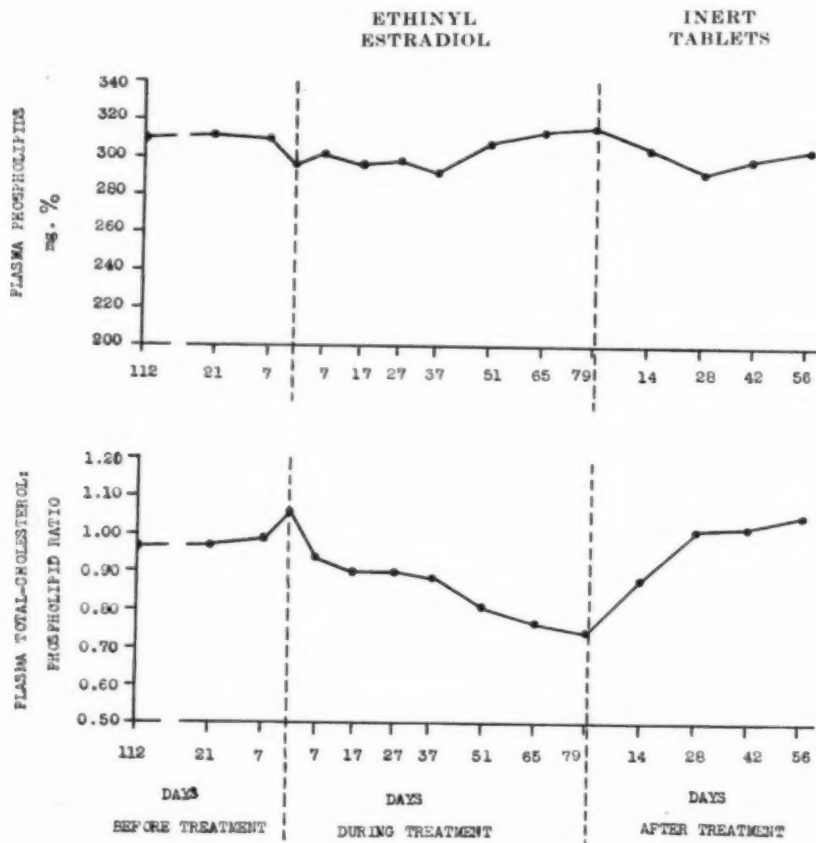

Fig. 3.—Long-term study.   The effect of ethinyl estradiol on the plasma phospholipids and the plasma total-cholesterol:phospholipid ratio.

   CASE 4.—S.S., aged 47, was a shipwright until 4½ years ago, subsequently a clerk.   Intermittent claudication for 4½ years had been evident, and angina for 9 months.   His electrocardiogram showed resting myocardial ischemia with no infarct.   Blood pressure was 168/100 mm. Hg.   Maximum dose of ethinyl estradiol 0.6 mg. daily; optimum dose, 0.4 mg. daily.   Gynecomastia, dizziness, depression and headaches developed; no nausea.   Weight loss was 2½ kg. during therapy.   Grade 2 before and after treatment.   His best fortnight for months coincided with the start of the inert pills.   Plasma total cholesterol fell by 22 per cent of the control value.

   CASE 5.—J.P., aged 67, a retired mill worker.   Extensive posterior infarct noted 4 years before treatment and was preceded by increasing breathlessness for 2 years; acute coronary insufficiency developed 10 and 8 months before treatment.   Blood pressure was 140/80 mm. Hg.   Maximum and optimum dose of ethinyl estradiol, 0.5 mg. daily.   No gynecomastia.   Nausea.

No weight change occurred during therapy. Grade 2 before and during treatment, with some improvement in effort tolerance. He died very suddenly at home on the day after estrogens were stopped; the classical pain of coronary thrombosis for 4 hours was followed by collapse. No autopsy. Plasma total cholesterol fell by 21 per cent of the control value.
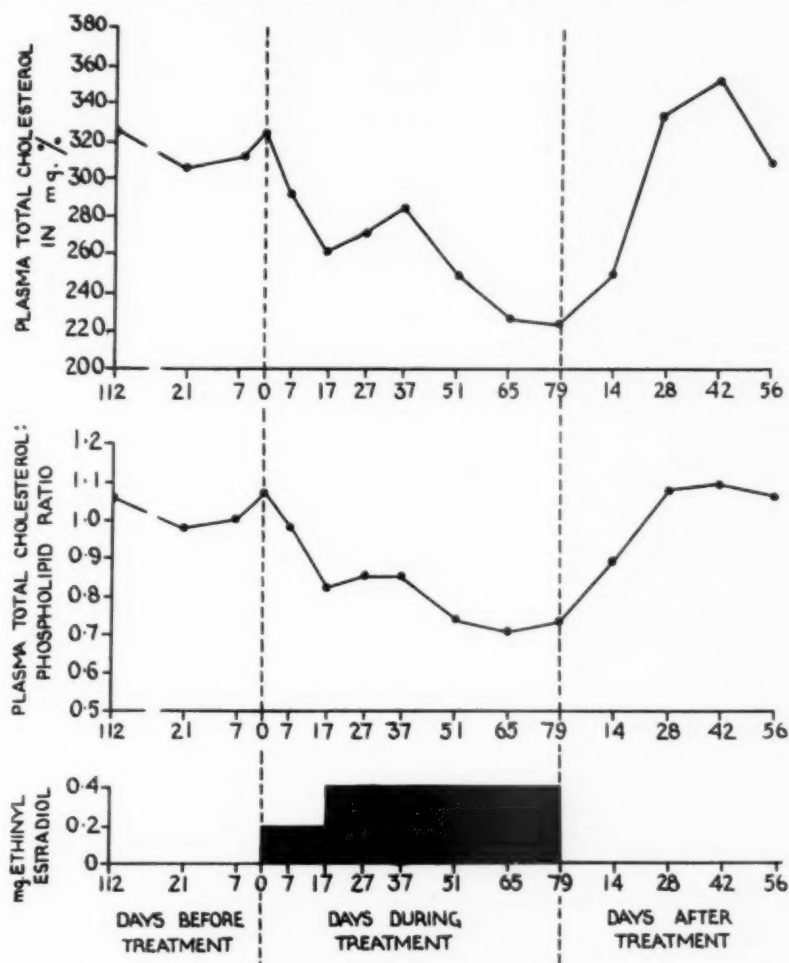

Fig. 4.—Long-term study. A typical subject, A. N., aged 49. The effect of ethinyl estradiol on the plasma total cholesterol and the plasma total-cholesterol:phospholipid ratio.

CASE 6.—S.Q., aged 37, a miner until the first infarct and driver of light pit engine subsequently. This posterior infarct occurred 4 months before treatment. Blood pressure was 160/96 mm. Hg. Maximum and optimum dose of ethinyl estradiol, 0.4 mg. daily. Gynecomastia but no nausea. Weight showed no change during therapy. Grade 2 before and during treatment. Extensive anteroseptal infarct developed two days after starting inert pills. He died 8 days later. Autopsy showed both infarcts but did not reveal any demonstrable cause for sudden death in the coronary, pulmonary, or cerebral circulations. Plasma total cholesterol fell by 41 per cent of the control value.

CASE 7.—L.E., aged 33, a clerk had angina for one week followed by an anteroseptal infarct 10 months before treatment. His blood pressure was 130/80 mm. Hg. Maximum and optimum dose of ethinyl estradiol, 0.4 mg. daily. Gynecomastia, loss of libido, and an ache in right testis

which spread toward right iliac fossa developed during the first two weeks, then an ache in the left testis, then both, for the rest of the estrogen course; no nausea. No weight change was noted during therapy. Grade 2 before and after treatment, with considerable improvement in effort tolerance. Plasma total cholesterol fell by 16 per cent of the control value.
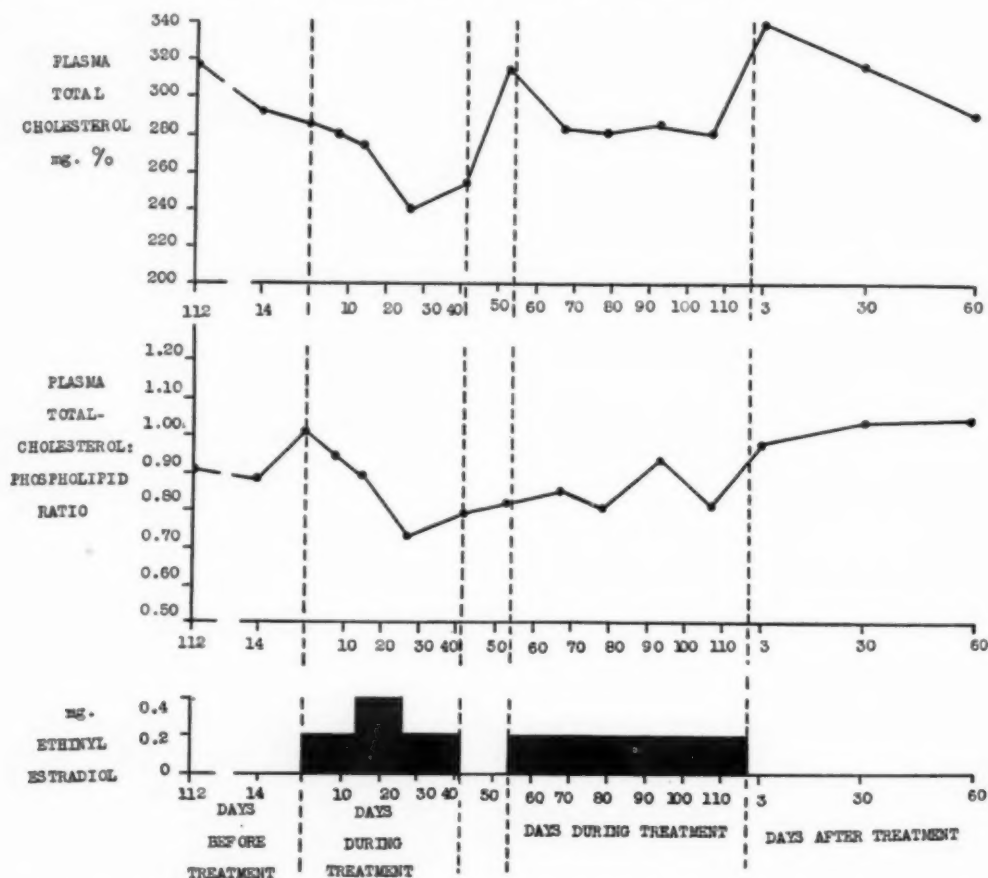

Fig. 5.—Long-term study. T.McD., aged 52. Plasma total cholesterol and plasma total-cholesterol: phospholipid ratio in a subject who twice exhibited intolerance to ethinyl estradiol.

CASE 8.—M.D., aged 53, an ice cream shop proprietor, had angina for 4 years followed by an extensive anterior infarct 10 weeks before therapy. Blood pressure was 110/70 mm. Hg. Maximum and optimum dose of ethinyl estradiol, 0.4 mg. daily. Gynecomastia, listlessness, fatigue and depression developed but no nausea. His weight showed a gain of 2½ kg. during therapy. Grade 2 before and after treatment. Plasma total cholesterol fell by 24 per cent of the control value.

CASE 9.—G.K., aged 63, a commercial traveller, had angina for 1½ years. His electrocardiogram showed myocardial ischemia at rest. His blood pressure was 170/96 mm. Hg. Maximum and optimum dose of ethinyl estradiol, 0.4 mg. daily. Gynecomastia developed but no nausea. No weight change was seen during therapy. Grade 2 before and after treatment with considerable improvement in effort tolerance. Plasma total cholesterol fell by 26 per cent of the control value.

CASE 10.—R.McG., aged 37, a plasterer, had angina for 4 days followed by an extensive posterior infarct 10 weeks before treatment. Blood pressure was 124/80 mm. Hg. Maximum

and optimum dose of ethinyl estradiol, 0.2 mg. daily. Gynecomastia and loss of libido developed but no nausea. A weight loss of 0.5 kg. occurred during therapy. Grade 2 before treatment and Grade 1 after treatment. He returned to full work and overtime, completely free from pain and very well. Plasma total cholesterol fell by 32 per cent of the control value.

CASE 11.—S.D., aged 44, a draper had angina for 3 months followed by a high anterolateral infarct 10 weeks before treatment. Blood pressure was 112/70 mm. Hg. Maximum dose of
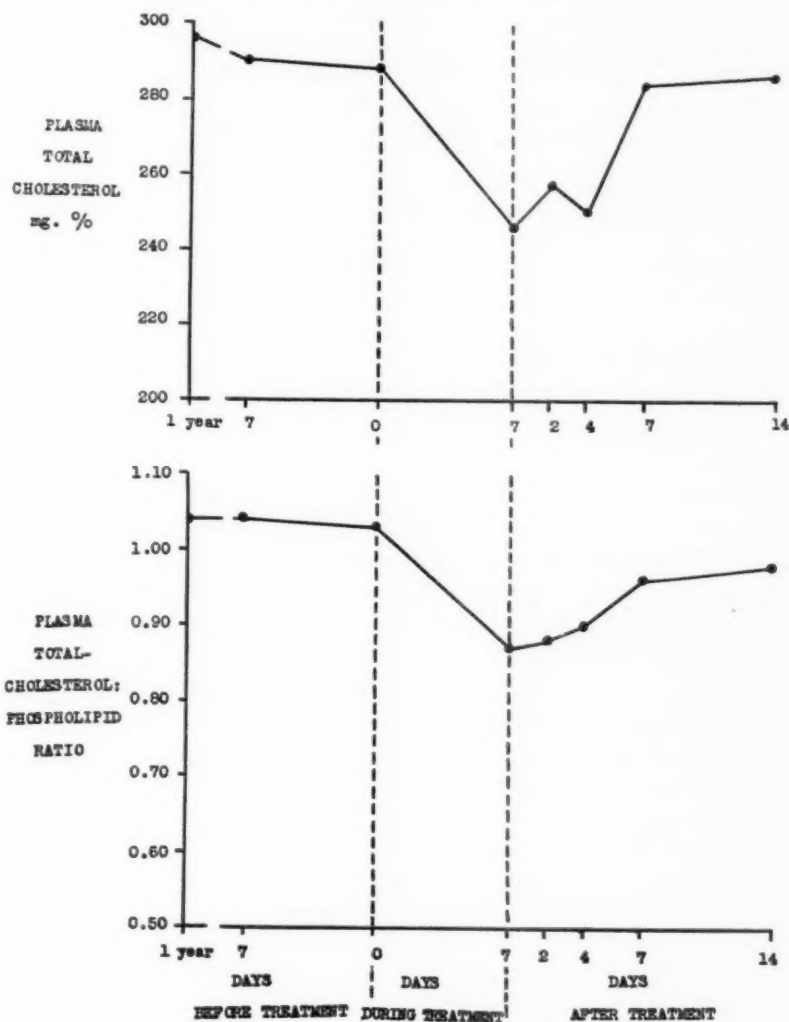

Fig. 6.—Short-term study. The effect of 1 mg. of ethinyl estradiol daily for 7 days on the plasma total cholesterol and plasma total-cholesterol:phospholipid ratio.

ethinyl estradiol, 0.4 mg. daily; optimum dose 0.3 mg. daily. Gynecomastia, loss of libido, and nausea developed. Weight loss was 1 kg. during therapy. Grade 2 before treatment and Grade 1 afterwards. Plasma total cholesterol fell by 26 per cent of the control value.

CASE 12.—A.M., aged 49, a cinema engineer, had angina for 4 years followed by an anterolateral infarct 15 months before treatment. His blood pressure was 112/74 mm. Hg. Maximum and optimum dose of ethinyl estradiol, 0.4 mg. daily. Gynecomastia and loss of libido with

psychological change were exemplified by a complete loss of interest in films of romantic appeal; no nausea. No weight change occurred during therapy. Grade 2 before and after treatment. An improvement in effort tolerance was noted. Plasma total cholesterol fell by 31 per cent of the control value.

CASE 13.—G.K., aged 40, was a long distance lorry driver until infarct, now is a clerk. He had an anteroseptal infarct one year before treatment, and a posterior infarct 3 months before treatment. Blood pressure was 108/70 mm. Hg. Maximum and optimum dose of ethinyl estradiol, 0.04 mg. daily. Gynecomastia, loss of libido, and nausea developed. No weight change was evident during therapy. Grade 2 before and after treatment but effort tolerance reduced. Plasma total cholesterol fell by 9 per cent of the control value.

CASE 14.—(See Fig. 5), T.McD., aged 52, was a tram driver before infarct, then did light work in a brewery. He had angina for 2 weeks followed by a posterior infarct 9 months before treatment. Blood pressure was 118/72 mm. Hg. Maximum dose of ethinyl estradiol, 0.04 mg. daily, with no optimum dose. Gynecomastia, depression, nausea, and vomiting developed. He was a migrainous subject who had two severe episodes of migraine each necessitating cessation of treatment. Weight gain was 1 kg. during therapy. Grade 2 before and after treatment. Plasma total cholesterol fell by 16 per cent of the control value during the first course.

CASES 15 TO 20.—These hypercholesterolemic men between 40 and 67, all of whom had proved myocardial infarction, received 1 mg. ethinyl estradiol daily for 7 days without any side effects, or change in their symptoms.

DISCUSSION

The results of this study have shown that small oral doses of ethinyl estradiol administered to hypercholesterolemic men with coronary artery disease effected marked depression of plasma ester cholesterol. Since the plasma phospholipids remained more or less constant, the plasma total-cholesterol:phospholipid ratio was also depressed. All the subjects developed side effects after two or three weeks' therapy. Gynecomastia, nausea, dizziness, listlessness, fatigue, and depression were common complaints; loss of libido occurred in some subjects and a subtle psychological feminizing change in one subject. Any of these features were regarded as a contraindication for increasing the dosage, and, indeed, they may preclude the widespread trial of estrogens per se in order to depress plasma cholesterol. All subjects who received inert tablets following estrogen therapy experienced a sense of well-being, and some reported increased energy and a return of libido. There was no definite over-all change in incidence, or severity, of effort pain or breathlessness; the majority were in functional Grade 2 before starting estrogens and remained in Grade 2 during and after treatment.

The comparative rarity of overt atherosclerosis in women before the menopause has been a source of speculation for years, yet few firmly based explanations have emerged; however, valuable information has been gained from the histological approach. It has been shown that the intima of male infants is thicker than the intima of female infants, a basic difference which may be anatomical[7] or pathological[10] in nature. If this difference persists into adult life it may favor the earlier development of atherosclerosis in the male. However, atherosclerotic lesions are present in the coronary arterial intima in premenopausal women. Indeed Lober[15] has suggested from histologic studies that these women may have as much as 75 per cent of the atheroma present in men of similar age; nevertheless, this degree of atheroma is apparently insufficient to produce symptoms. The increase in the incidence of atherosclerosis after the menopause suggests that

its development may be influenced by decreased gonadal function.   In support of this it has been shown that bilaterally oophorectomized women show more atherosclerosis than normal women of corresponding age.[31]   Much interesting work concerning the association of estrogens and atherosclerosis has been done in the chick, but at present it is somewhat difficult to interpret it in the light of human atherosclerosis.   It has been shown that large implantations of estrogens (diethylstilbestrol) produced lipemia in the chick,[9,16] and Chaikoff and associates,[5] and Horlick and Katz[13] have demonstrated that this lipemia is associated with an increase in atheroma.   These experiments suggest that estrogen implants potentiate atherosclerosis in the bird receiving a normal diet.   It is well known that cholesterol will induce atherosclerosis in the chick, and recently it has been shown that the administration of estrogens to chicks receiving cholesterol in their diet will inhibit atherosclerosis.[14,22,23]   Moreover, Pick and associates[25] have demonstrated that estrogens will cause regression of previously induced coronary lesions despite continued feeding with cholesterol.   Thus, in the chick, estrogens alone and cholesterol alone induce atherosclerosis, but when combined, estrogens apparently antagonize the atherogenic property of cholesterol.

The histologic approach is obviously impossible in the living subject, but there is strong evidence to suggest that coronary atherosclerosis is associated with elevation of the plasma lipids.[11,18,21,29]   Since the atheromatous plaques are probably derived in part from the plasma lipids, it is of interest to study the plasma lipids in relation to the low incidence of atherosclerosis in premenopausal women, and, in particular, to the question of the hormonal influences involved in lipid metabolism.   In a study of the plasma lipids in a small group of normal women before and after the menopause it has been shown that there was a tendency for the plasma lipids of postmenopausal women to be higher than those prevailing in premenopausal women.[21]   Such a postmenopausal rise in the plasma lipids may be related to the withdrawal of estrogenic hormones at the menopause.   Cyclical changes have been observed in plasma total cholesterol and the plasma total-cholesterol: phospholipid ratio during the menstrual cycle in normal young women, and it has been suggested that the depression of these values at ovulation might be related to the maximal estrogen secretion at that time.[20]   Moreover, Eilert[8] has shown that the plasma total cholesterol was depressed and the plasma phospholipids were elevated in women who received small dosages of estrogens; in contrast no elevation in the plasma phospholipids was observed in this study of men with coronary artery disease.

The experimentally induced coronary lesion in chicks and the elevated plasma lipids in human coronary artery disease both appear to be beneficially influenced by estrogens.   The precise mechanism of these effects has not yet been established but many possibilities are open to speculation.   Since the plasma lipids are both synthesized and degraded in the liver, the ultimate control of these lipid levels is probably mediated through this organ.   It may well be that estrogens per se have no direct effect on the plasma lipids or the liver, but that their action is achieved through other target organs such as the anterior pituitary,[4] which in turn influences the thyroid and the adrenal cortex.   Recently it has been suggested that the antiatherogenic effect of estrogens observed in chicks is inde-

pendent of the presence of functioning gonads.[24]   Thus, there is at present no conclusive evidence regarding the intermediate steps by which estrogens depress plasma cholesterol.

It appears that estrogens may have an antiatherogenic action in chicks and that the presence of estrogens may be of fundamental importance to the relative immunity of premenopausal women to clinical coronary artery disease.   The combination of androgens with estrogen therapy, which has recently been said to diminish the feminizing tendency in male chicks without inpairing the anti-atherogenic activity,[28] may allow more extensive investigation and clarification of the therapeutic application of estrogens to established coronary artery disease in the human being.

SUMMARY

1.   Small doses of ethinyl estradiol depressed the plasma ester cholesterol in twenty hypercholesterolemic men with coronary artery disease.   As the plasma phospholipids were uninfluenced, the plasma total-cholesterol:phospholipid ratio was also depressed.

2.   Some aspects of the role of the estrogenic hormones in lipid metabolism and atherosclerosis are discussed.

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A NEW SYNTHESIS OF SOME OF THE PHYSICAL FOUNDATIONS OF CLINICAL ELECTROCARDIOGRAPHY

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EXPERIMENTS have shown that cardiac muscle produces a flow of electric current in surrounding media. The activated region, as it travels along, has an invading boundary and a retreating boundary. At the invading boundary there are simultaneous anodes and cathodes so oriented that the anodes are in the lead. Over the boundary of retreat are other anodes and cathodes with the cathodes in the lead. The combination of an anode and a cathode constitutes a dipole. Consequently, the external field of current flow around excited muscle may be ascribed to dipoles of invasion and dipoles of retreat.[1]

The physics of electric dipoles is well known.[2] Let l be the distance between the two charges of a dipole. Let q and − q be the two charges on the dipole. They are of equal magnitude but of opposite sign (Fig. 1.). The product ql is known as the electric moment of the dipole. The electric moment is a vector having the direction of the axis of the dipole. We take its sense to be that of the line from − q to q. Let p = ql and let r be the distance from the center of the dipole to the point where the potential, V, is being measured. Let the line between the point where the potential is being measured and the dipole make an angle θ with the electric moment of the dipole. Then it can be proved that

$$V = p \cos \alpha/r^2. \tag{1}$$

The numerator of the expression for V is the component of the electric moment in the direction of r. The expression given for V is only true when r is very much greater than l. The expression (1) is ordinarily derived for charges on a dipole immersed in a nonconductor. Although the human body is immersed in a volume conductor rather than in a nonconductor, with experimental justification[3] the same reasoning has been applied in the latter situation. Actually in the physiologic situation each elemental dipole consists of a cathode and an anode immersed in a conducting medium with a current flowing between them. The term and concept of electric moment have not been used by electrocardiographic investigators commonly enough when discussing the quantitative aspects of electrical activity of the heart. For exact study, electric moment is a useful quantity. Einthoven[4] instead spoke of the manifest potential difference.

The basis of modern clinical electrocardiography is founded in large part upon the Einthoven triangle hypothesis.[4]   The human body is represented as a flat, homogeneous plate in the form of an equilateral triangle.   Current is let off to the galvanometer from the corners (Fig. 2).   R is the right arm, L is the left arm, and F represents the legs.   A small spot in the middle of the triangle represents the heart.   Between two closely adjacent points of the small spot a potential difference is developed.   The line joining these two points represents the direction of the maximum potential difference in the heart or, in more correct physical terms, the direction of the electric moment.   The distance separating the points is very small compared with the length of one side of the triangle. The angle that the arrow makes with the side RL is α and is reckoned as positive when the arrow is turned in the clockwise direction.   In determing this, the standpoint of an observer facing the anterior chest wall of the subject is assumed. Fig. 2 is Einthoven's drawing.
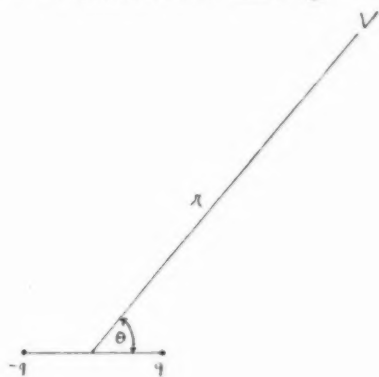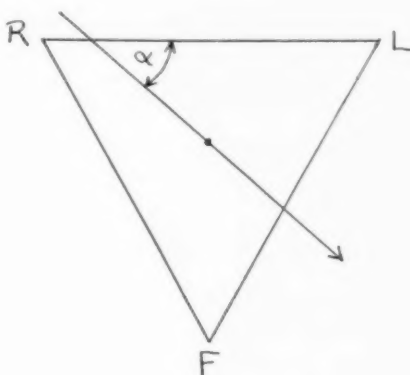

Fig. 1.   Fig. 2.

Fig. 3 permits a better visualization.   VR, VL, and VF are, respectively, the potentials at the right arm, the left arm, and the left leg (which is assumed to equal that of the pubis or right leg) due to the electric moment p (which is a vector quantity).   The electric moment, p, makes an angle α with the line connecting VR and VL.   It is assumed that the heart is an equal distance r from R, L, and F.   Then it follows that

$$VL = p \cos (\alpha + 30°)/r^2 = p (\sqrt{3} \cos \alpha - \sin \alpha)/2r^2, \qquad (2)$$
$$VR = p \cos (\alpha + 150°)/r^2 = - p (\sqrt{3} \cos \alpha + \sin \alpha)/2r^2, \qquad (3)$$

and

$$VF = p \cos (90° - \alpha)/r^2 = p \sin \alpha/r^2. \qquad (4)$$

I, II, and III are defined as the potentials recorded by the standard limb leads of the electrocardiogram.   Then, using (2), (3), and (4),

$$I = VL - VR = \sqrt{3}p \cos \alpha/r^2, \qquad (5)$$
$$II = VF - VR = p(3 \sin \alpha + \sqrt{3} \cos \alpha)/2r^2, \qquad (6)$$

and

$$III = VF - VL = p(3 \sin \alpha - \sqrt{3} \cos \alpha)/2r^2. \qquad (7)$$

The vector p constantly changes in magnitude and direction. Its path, when graphically portrayed, describes a looplike figure during the cardiac cycle. This path is known as a vectorcardiogram.

The relationship of the standard limb leads (I, II, and III) and the unipolar extremity leads (VL, VR, and VF) to each other and to the electric moment produced by the heart is important. The unipolar limb leads are recorded differently than are the standard limb leads, and they cannot properly be compared vectorially, when uncorrected, with the latter in relation to the electric moment of the heart. The Einthoven triangle may be replaced by a triaxial reference system formed by translating the sides of the triangle in such a way that the midpoints of the sides coincide at a common point, the origin 0.[5] This can be considered
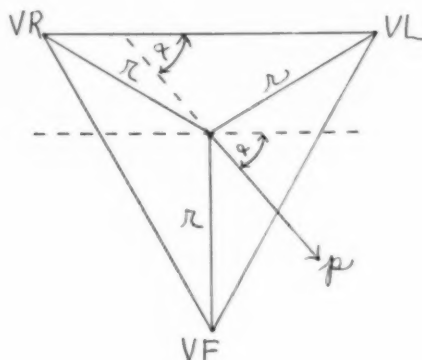

Fig. 3.

equivalent to taking leads along the axes having the same direction as the standard limb leads but using the unipolar method (Fig. 4). These leads are readily compared with the unipolar extremity leads. Electrodes are placed a distance from the heart along the directions indicated in Fig. 4 and the symbols for their potentials defined there. It is seen that

$$VI = p \cos \alpha/r^2, \tag{8}$$
$$VII = p \cos(60° - \alpha)/r^2, \tag{9}$$

and

$$VIII = p \cos(120° - \alpha)/r^2, \tag{10}$$

but comparing (5), (6), and (7) with (8), (9), and (10) it is obvious that

$$I = VL - VR = \sqrt{3}VI, \tag{11}$$
$$II = VF - VR = \sqrt{3}VII, \tag{12}$$

and

$$III = VF - VL = \sqrt{3}VIII. \tag{13}$$

Consequently, we may conclude that the same magnitude of the cardiac vector or electric moment produced by the heart may be obtained from the unipolar limb leads as from the standard limb leads if the values obtained in the unipolar limb leads are multiplied by $\sqrt{3}$. This was shown by Hill[6] and emphasized by Graettinger and associates.[7] The latter mentions in an addendum to

his paper[7] included on his reprint that one manufacturer now makes a model of its electrocardiographic instrument with a lead selector switch permitting the recording of unipolar limb leads multiplied by $\sqrt{3}$ (called vVL, vVR, and vVF) without changing the sensitivity of the electrocardiograph during the tracing. The more popular augmentation method used on most apparatus is that of Goldberger,[8] where the augmentation factor for the unipolar extremity leads is 1.5 rather than $\sqrt{3} = 1.732$.
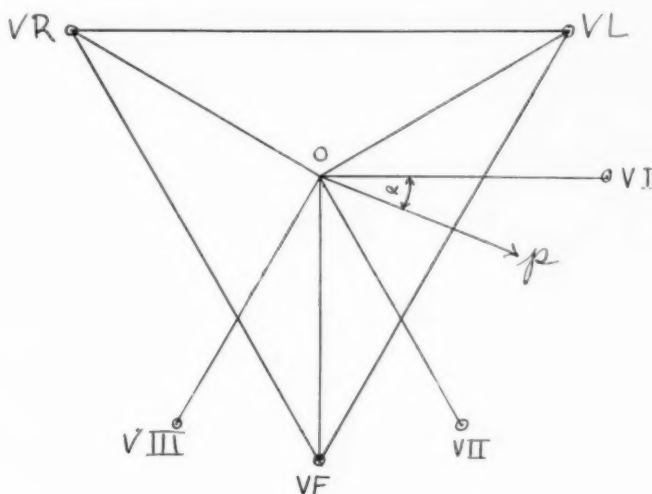

Fig. 4.—The electric dipole p is situated at the origin O. The letters adjoining the symbol ° represent potentials at those points due to p.

From the previous discussion the conclusion follows that there is no particular superiority of the unipolar limb leads over the standard limb leads. Each system of leads gives the projection of the electric moment of the heart along three axes 60° apart. The same information is provided by either set of leads. The advantage of the standard limb leads is the greater familiarity of most persons with them because they have been in use for a greater period of time.

A vital problem in the use of the unipolar leads is the provision of a terminal of zero potential. The best presently available answer to this was given by Wilson and associates[9] (Fig. 5). Let VT be the potential of the central terminal and R be the magnitude of three equal resistances. Wilson used 5,000 ohm resistances. If the potentials of the three terminals are VR, VL, and VF and the currents flowing from these electrodes towards the central terminal are IR, IL, and IF, then by Ohm's law[10]

$$VR - VT = R(IR), \tag{14}$$
$$VL - VT = R(IL), \tag{15}$$

and

$$VF - VT = R(IF). \tag{16}$$

If (14), (15), and (16) are added, there is obtained

$$(VR - VT) + (VL - VT) + (VF - VT) = R(IR + IF + IL). \quad (17)$$
$$IR + IF + IL = O, \quad (18)$$

since the algebraic sum of all currents meeting at any point of a network is zero according to Kirchoff's laws. Then

$$VT = (VR + VL + VF)/3, \quad (19)$$

but by adding (2), (3), and (4), it is found that

$$VR + VL + VF = O. \quad (20)$$

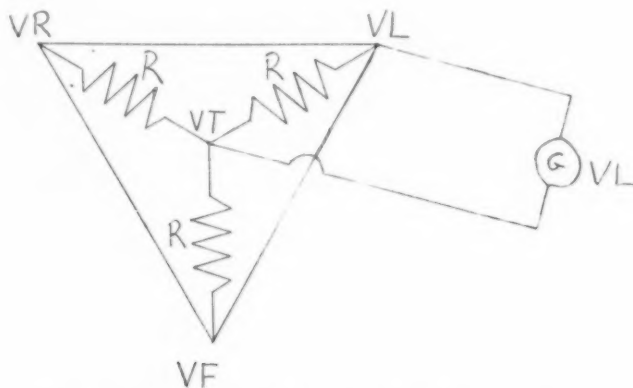Consequently by substituting (20) in (19),

$$VT = O. \quad (21)$$

Fig. 5.—Lead V_L is being recorded by the galvanometer G.

In the Wilson central terminal the purpose of the resistors in each limb circuit is to minimize differences in subject resistance at each limb.   Dissimilarity in contact resistance of each limb introduces variations in current distribution in the central terminal circuit, which affects the potential of the central terminal.[12] By Ohm's law

$$V = IR,$$

where V is potential difference, I is current flowing from one point to the other point between which the potential difference exists, and R is the resistance between the two points.   Let R be 5,000 ohms.   Then

$$V = 5,000I_o,$$

where I_o is the current flowing across a resistance of 5,000 ohms with an applied potential V.   Suppose skin resistance is 1,000 ohms; then

$$V = (5,000 + 1,000)I_1 = 6,000I_1,$$

where I_1 is the current flowing across a resistance of 6,000 ohms with a potential V applied.   Compared with I_o (= $V/5,000$), I_1 (= $V/6,000$) is 83.3 per cent of

what it would be if the skin had no resistance. Suppose that instead of using R = 5,000 ohms in the central terminal, R = 1,200 ohms is used in the central terminal. V, I_o, and I_1 are defined as before. Then

$$V = 1,200 I_o.$$

Again, if skin resistance is 1,000 ohms,

$$V = 2,200 I_1.$$

Compared with I_o (= V/1,200), I_1 (= V/2,200) is 54.5 per cent of what it would be if skin resistance were zero. Consequently, it follows that, if the resistors in the central terminal are made smaller, the variations in current flow due to non-zero skin resistances of equal magnitude are much larger with the smaller central terminal resistors.
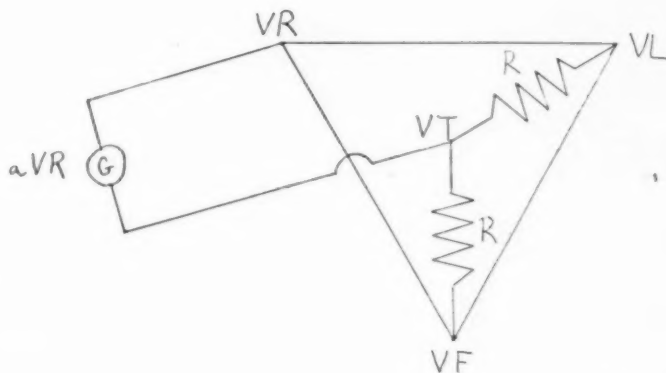
Fig. 6.—Lead aV_R is being recorded by the galvanometer G.

Goldberger[8] designed a central terminal omitting the resistors used by Wilson. To augment the amplitude of the unipolar extremity leads, the electrode from the central terminal was kept off the extremity from which a record was being taken (Fig. 6). Goldberger[8] states that, if the augmented right arm lead is being taken, the potential of the central terminal is equal to

$$(VL + VF)/2 \text{ or } - VR/2,$$

since

$$VR + VL + VF = 0$$

or

$$VL + VF = - VR,$$

and consequently,

$$(VL + VF)/2 = - VR/2.$$

The record so obtained would be equal to

$$VR - (- VR/2) = 3VR/2. \tag{22}$$

The leads aVR, aVF, and aVL can then be defined as

$$aVR = 3VR/2, \tag{23}$$
$$aVL = 3VL/2, \tag{24}$$
$$\text{and}$$
$$aVF = 3VF/2. \tag{25}$$

Although Goldberger[8] merely states without proof that $(VR + VF)/2$ is the potential of his central terminal used in obtaining lead aVL, this observation can readily be proved by Kirchoff's law.   By referring to Fig. 6 and applying Ohm's law,

$$VL - VT = R(IL) \tag{26}$$

and

$$VF - VT = R(IF). \tag{27}$$

Adding (26) and (27),

$$(VL - VT) + (VF - VT) = R(IL) + R(IF). \tag{28}$$

But, by Kirchoff's law

$$IL + IF = O. \tag{29}$$

Then substituting (29) in (28),

$$VL + VF = 2VT$$

and so

$$VT = (VL + VF)/2. \tag{30}$$

Einthoven's law[4] states that

$$I + III = II. \tag{31}$$

By substituting in (31) the definitions of I, II, and III given in (5), (6), and (7),

$$(VL - VR) + (VF - VL) = VF - VR, \tag{32}$$

which reduces to

$$VF - VR \equiv VF - VR,$$

which is an identity, proving Einthoven's law.   It can be readily seen that Einthoven's law is not true by reason of the equilaterality of the triangle used but is a consequence of the simple principle[13] that a direct measurement of the potential between two points will give the same result as an indirect measurement in which the potential of each point is compared to a third point.

COMMENTS AND SUMMARY

The physical concepts of electric dipole and electric moment vector are valuable in studying the electrical activity of the heart.   The magnitude of the electric moment of an electric dipole is the product of the magnitude of its charges

and the distance between the charges.   An equation gives the magnitude of the potential produced by an electric dipole at any point in its field.   The resultant of the electrical activity of the heart is represented as an electric moment changing in magnitude and direction.   The vectorcardiogram is a graphic portrayal of the constantly changing magnitude and direction of the electric moment of the heart.

The Einthoven triangle hypothesis is restated in more modern terms.   On this basis the standard limb leads and the unipolar extermity leads are defined. A new demonstration of the quantitative relationship between the unipolar extremity leads and the standard limb leads is given.   The concept that the unipolar limb leads and the standard extremity leads merely represent the projections of the same cardiac vector (more correctly the electric moment) on axes differently positioned is emphasized.   The discussion makes clear that neither set of leads really furnishes any information not inherent in the other set and that both individually furnish an equal amount of information.

The basis of Wilson's central terminal for unipolar leads is given and compared with Goldberger's terminal for deriving the augmented limb leads.   The value of the resistors in the central terminal is explained and the errors produced in removing them are discussed.   Some of Goldberger's mathematical expressions essential in defining the augmented limb leads and for which no previous justification has been given are proved here.

Wilson's simple proof of Einthoven's law is given.   This concept can be extended to three or more points in any relationship to each other.[6]

The validity of the original assumptions made by Einthoven is assumed. Consequently, the conclusions resulting from these assumptions are correct only insofar as these assumptions are a good approximation of the actual situation. It appears that the assumptions are a good approximation because they are basic to modern clinical electrocardiography, and clinical electrocardiography has proved to be an immensely useful tool in medicine.

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A CORRELATION OF THE SPATIAL VECTORCARDIOGRAM WITH RIGHT VENTRICULAR HYPERTROPHY

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D IRECT spatial vectorcardiography is a method for recording the propagation of the electromotive forces of the cardiac musculature in several planes. The vectorcardiogram is a projection on an oscilloscope of the time course of the instantaneous electrical axes of the heart. The action currents of the heart at each instant during depolarization and repolarization produce electromotive forces the sum of which is a vector quantity. The termini of the instantaneous vectors describe a loop during the time consumed by ventricular activation. The theoretical basis for the spatial vectorcardiogram has been fully discussed by Duchosal and Sulzer,[1] and Grishman and Scherlis.[2]

Grishman and Scherlis,[2] using their modified Duchosal-Sulzer cube placement,[1] have shown that the vectorcardiogram has distinctive features in right ventricular hypertrophy. These consist of changes in the form, orientation, and rotation of the vector loops in all three planes, namely, horizontal, frontal, and sagittal. In right ventricular hypertrophy, the vector loop in the horizontal plane rotates in a clockwise direction, the centrifugal portion of the loop being posterior to the centripetal limb. A large portion of the loop is inscribed to the right of the E point, the long axis lying mostly in sextants III, IV, or V of the triaxial reference system of Bayley.[3] The frontal and sagittal planes of the vector loops show a shift to the right and an anterior displacement. On the other hand, in the normal heart in the horizontal plane the vector loop leaves the E point traveling slightly to the right and anteriorly,* shortly turning to the left and moving in a counterclockwise direction for a variable distance; the centripetal limb turns posteriorly to return to the E point. Almost all of the loop is inscribed to the left of the E point, the long axis being either in sextant VI or I. The centrifugal limb is always anterior to the centripetal limb.[2]

The reported studies of Lasser and associates[4] on right ventricular hypertrophy in twenty-five cases ranging in age from three to thirty-two years were done in patients with congenital heart disease, including isolated pulmonary stenosis, pulmonary stenosis with interatrial septal defect, tetralogy of Fallot,

*Right, left, anterior, posterior refer to the patient's right, left, etc.

Eisenmenger's complex, interatrial septal defect, and Lutembacher's syndrome. Right ventricular and pulmonary artery pressures were recorded in most of their patients but right ventricular work was not calculated.   However, apparently no cases of acquired heart disease with right ventricular hypertrophy were studied.

The purpose of this study is to correlate the direct spatial vectorcardiogram in patients with congenital heart disease and acquired heart disease, that is mitral stenosis, with right ventricular pressures and right ventricular work.

MATERIALS AND METHODS

The subjects were patients in the clinics and wards of the Los Angeles County Hospital.   Thirty-four patients were selected on whom cardiac catheterization had been performed or was contemplated.   The basis of selection was the presence of isolated right ventricular hypertrophy suspected clinically or demonstrated by cardiac catheterization.   Patients with clinical evidence of left ventricular hypertrophy were excluded.   Sixteen had mitral stenosis and eighteen had congenital heart disease.   The ages varied from three to fifty-three years; fifteen were females and nineteen were males.   None of these patients had had congestive heart failure for at least two weeks prior to cardiac catheterization or vectorcardiographic recording.

The catheterization data consist of: (1) right ventricular and pulmonary artery systolic pressures as determined by a strain gauge manometer; (2) cardiac output as determined by the Fick principle during cardiac catheterization.   The measurement of right ventricular work was obtained by the use of the formula of Gorlin and associates:[5]

$$W_R = \frac{(\text{Cardiac index} \times 1.055)\,(PA_m - RA_m \times 13.6)}{1000} \text{ kg. M. per minute per sq. M.}$$

For all patients, right ventricular mean systolic ejection pressure was substituted for mean pulmonary artery pressure (PA_m) and was measured according to the method of Gorlin and Gorlin[6] by planimetric integration.   In this manner calculations in mitral stenosis and congenital heart disease were rendered comparable; this substitution was necessary because of the frequent presence of pulmonary stenosis.   Right ventricular work greater than 1.0 kg. M./min./sq.M.* was considered abnormal.[7]

Electrocardiograms were taken with both direct-writing and string galvanometer instruments at normal speeds.   In addition to the conventional leads, Lead V_{3R} was taken on all patients except one; in one-third of the patients Leads V_{4R} and V_{5R} were recorded.   In most of the patients the vectorcardiograms were taken three to six months after cardiac catheterization, while in the remaining patients the vectorcardiograms were recorded one to two days before catheterization.   All the patients had cardiac fluoroscopic studies and many had angiocardiograms as well.   The diagnosis of right ventricular hypertrophy was made according to the criteria of Myers and co-workers.[8]

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*Hereinafter referred to as units.

The vectorcardiograms were obtained using the method described by Grishman and Scherlis,[2] based on their modification of the Duchosal-Sulzer cube arrangement[1] for the placement of the electrodes.   The polarity was adjusted as suggested by Grishman and Scherlis.[2]   Only one oscilloscope was used, so arranged that each plane could be obtained with push-button rapidity.   The vector loop was interrupted four hundred times per second by intensity modulation, permitting time analysis of the loop.   A camera was used to photograph the loops using fast film and employing time exposure.   In this manner, several loops in the same plane were recorded on the same film by moving the position of the loop on the face of the oscilloscope.

RESULTS

Tables I and II show the relationships between work and pressure levels in the right ventricle and the normal or abnormal vectorcardiograms and electrocardiograms.   The right ventricular work was used as a measure of right ventricular hypertrophy.

TABLE I.   MITRAL STENOSIS

PATIENT	AGE (YEAR)	VECTOR	ECG	MEAN RV PRESSURE*	RV WORK UNITS**
F.L.	50	N***	N	21	0.32
H.D.	36	N	N	23	0.56
B.L.	38	N	N	21	0.69
H.P.	35	N	N	17	0.71
J.L.	35	N	N	26	0.81
E.S.	53	N	N	54	1.01
H.N.	37	N	N	22	1.06
R.R.	38	RVH°	N	52	1.10
G.M.	35	RVH	IRBBB°°	66	1.29
H.A.	40	RVH	IRBBB	55	1.31
H.G.	37	RVH	IRBBB	85	1.50
D.A.	27	N°°°	IRBBB	57	1.73
C.M.	33	RVH	RVH	44	2.11
J.S.	27	RVH	N	42	2.59
F.H.	42	RVH	RVH	78	2.69
M.A.	32	RVH	RVH	85	3.03

*Mean right ventricular systolic ejection pressure (mm. Hg).
**Right ventricular work units. One unit equals 1 kg. M./min./sq. M.
***Normal.
°Right ventricular hypertrophy.
°°Incomplete right bundle branch block.
°°°Normal with terminal appendage.

Mitral Stenosis.—The sixteen patients with mitral stenosis (Table I) are tabulated in order of increasing right ventricular work.   Seven patients had a right ventricular work of 1.06 units or less with mean right ventricular systolic ejection pressure ranging from 17 to 26 mm. Hg with the exception of E. S. whose datum was 54 mm. Hg.   Nine patients had right ventricular work more than 1.06 units; the mean right ventricular pressure ranged from 42 to 85 mm. Hg. The vectorcardiograms were normal in all cases with right ventricular work 1.06

units or less.   The horizontal loop was diagnostic of right ventricular hypertrophy in eight of nine cases with right ventricular work greater than 1.06 units, with the one exception of patient D. A.   These loops showed clockwise rotation and increasing rightward and anterior deviation, the major portion of these loops appearing in sextants IV and V, whereas in the normal patient without heart disease the loops appear primarily in sextants I and VI.

In patients having right ventricular work less than 1.06 units, the frontal loops appear in sextant VI or the adjacent segment of V. When right ventricular work exceeded 1.06 units, an increasingly greater portion of the loop was seen in sextant V.   All these loops exhibited clockwise rotation, except for one patient, D. A., and also appeared wider and more orthogonal than the normal.

TABLE II.   CONGENITAL HEART DISEASE

PATIENT	DIAGNOSIS	AGE (YR.)	VECTOR	ECG	MEAN RV PRESSURE*	RV WORK UNITS**
R.W.	Pulmonary stenosis with interventricular defect	18	RVH°	N***	21	0.97
J.P.	Interventricular defect?	6	N	N	12	0.95
R.A.	Pulmonary stenosis	6	RVH	IRBBB°°	40	1.38
J.M.	Pulmonary stenosis with interauricular defect	23	RVH	RVH	30	1.42
M.B.	Pulmonary stenosis with interventricular defect	9	RVH	RVH	32	1.44
M.C.₃	Transposed pulmonary veins	25	N	N	21	1.99
L.S.	Pulmonary stenosis with interauricular defect	3	RVH	RVH	50	2.18
E.C.	Pulmonary stenosis	12	RVH	IRBBB	34	2.50
S.B.	Tetralogy of Fallot	20	RVH	RVH	66	3.67
M.L.	Pulmonary stenosis with interventricular defect	7	RVH	IRBBB	68	3.71
J.M.	Pulmonary stenosis	7	RVH	RVH	54	4.23
D.G.	? Eisenmenger	16	RVH	RVH	86	4.27
R.Wa.	Tetralogy of Fallot	10	RVH	RVH	71	4.63
E.D.	Transposed pulmonary veins	55	RVH	IRBBB	43	4.65
J.B.	? Eisenmenger	28	RVH°°°	RVH	64	5.30
J.S.	Tetralogy of Fallot	3	RVH	IRBBB	78	5.60
F.S.	Pulmonary stenosis with interventricular defect	30	RVH	RVH	82	6.19
R.K.	? Eisenmenger	7	RVH	RVH	76	7.55

Abbreviations same as in Table I.
°°°Also shows right bundle branch block.

When right ventricular work was less than 1.06 units, the sagittal loops rotated clockwise; when right ventricular work exceeded 1.06 units, they rotated counterclockwise except in one case (D.A.). They appeared more anteriorly oriented than the normal; however, in most instances the loops were narrow.

Of the nine patients with work level greater than 1.06 units, three patients showed the classical electrocardiographic pattern of right ventricular hypertrophy, four had the pattern of incomplete (partial) right bundle branch block, and two had normal electrocardiograms. The four patients with incomplete right bundle branch block exhibited right ventricular hypertrophy in the vectorcardiogram. In the two patients (R. R. and J. S.) with normal electrocardiograms, the right ventricular work was 1.10 and 2.59 units, respectively, and the mean right ventricular systolic ejection pressures were 52 and 42 mm. Hg, respectively. The vectorcardiograms of R. R. and J. S. were diagnosed as right ventricular hypertrophy. The vectorcardiogram was normal in patient D. A. who had incomplete right bundle branch block. Every patient with a normal right ventricular work level had a normal electrocardiogram.

Congenital Heart Disease.—In sixteen of the eighteen patients with congenital heart disease (Table II), the right ventricular work exceeded 1.06 units and the vectorcardiograms were diagnostic of right ventricular hypertrophy with the one exception of patient M.C. The direction and orientation of the loops were similar to that seen in mitral stenosis, except that in the horizontal plane there was more rightward deviation and eleven of the sixteen sagittal loops rotated clockwise in contrast to the patients with mitral stenosis. The mean right ventricular systolic ejection pressures ranged from 21 to 86 mm. Hg.

In ten of the patients with vectorcardiograms diagnostic of right ventricular hypertrophy, the electrocardiograms were also diagnostic of right ventricular hypertrophy. In addition, five patients showing vectorcardiograms of right ventricular hypertrophy had electrocardiograms of incomplete (partial) right bundle branch block.

In two patients (R. W. and J. P.), the right ventricular work was less than 1.06 units, and the electrocardiograms in both were normal. The vectorcardiogram of R. W. was interpreted as right ventricular hypertrophy while the vectorcardiogram of J. P. was normal. One patient (M. C.), with a high work level (1.99 units) had both a normal electrocardiogram and vectorcardiogram.

DISCUSSION

From Table I it is noted that the maximum right ventricular work in this series of patients with mitral stenosis was 3.03 units; whereas it was 7.5 units (Table II) in this series of patients with congenital heart disease, with ten patients having right ventricular work greater than 3.03 units. Lasser and associates[4] have shown that the horizontal plane loop in right ventricular hypertrophy becomes deviated to the right and that the QRS sÊ loop is in the upper right anterior octant or upper one-half of the lower right anterior octant. If a correlation exists between the amount of right ventricular work and right ventricular hypertrophy then it would be expected that in the series of congenital heart disease with the greater right ventricular hypertrophy, the vectorcardiogram would show

a greater deviation to the right in the horizontal loop than in mitral stenosis and that the spatial position of the QRS loop would be in the anterior right octant.
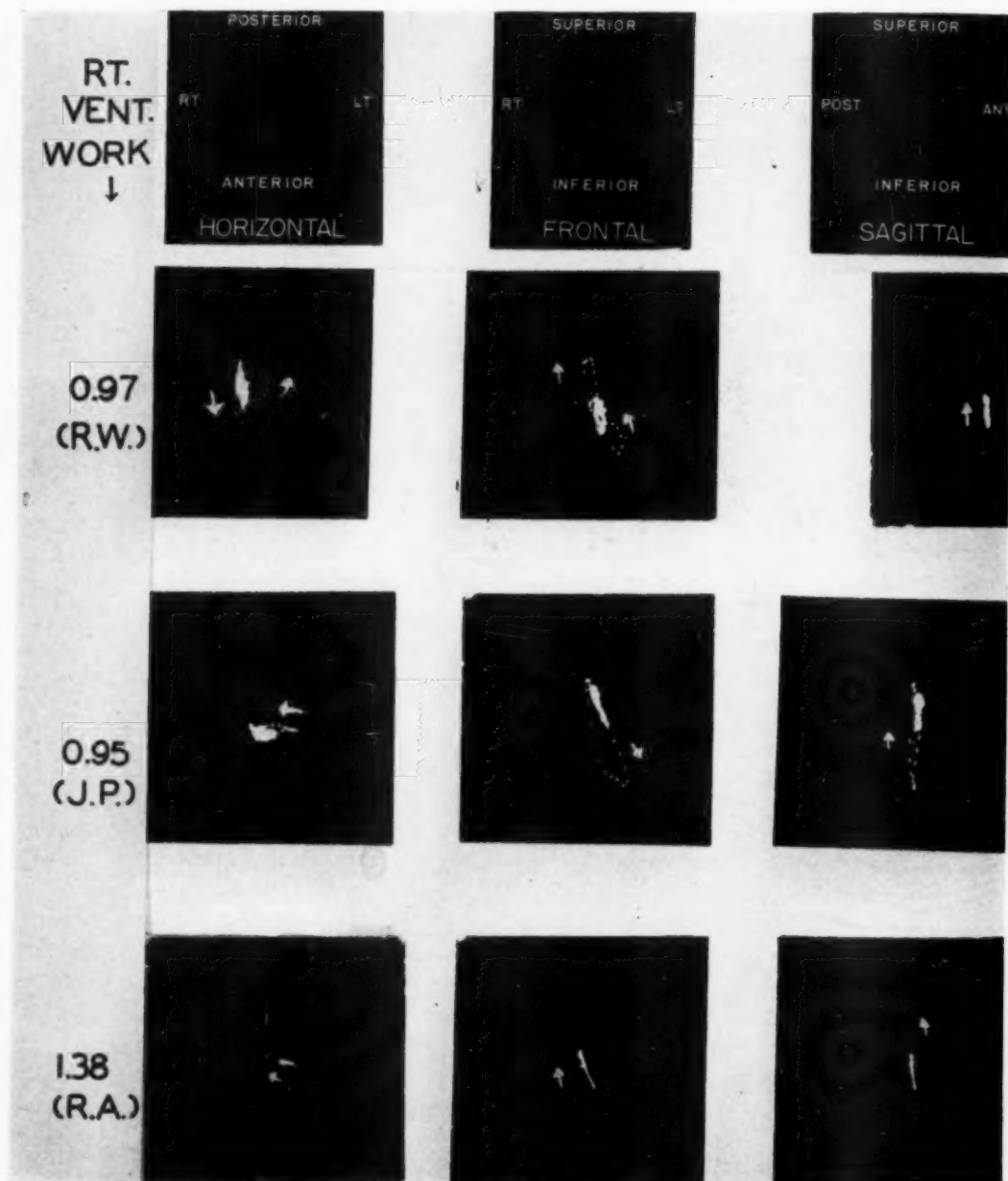

Fig. 1A.—Congenital heart disease arranged in order of increasing right ventricular work. See text and Table II.

This appears to be substantiated by Figs. 1A, 1B, 1C, which show that in congenital heart disease more than one-half of the horizontal loop extends to the right of the E point in sextants V and IV and the QRS sÊ loop is in the right anterior upper

or lower octant.   However, of the patients with mitral stenosis (Figs. 2A, 2B) only
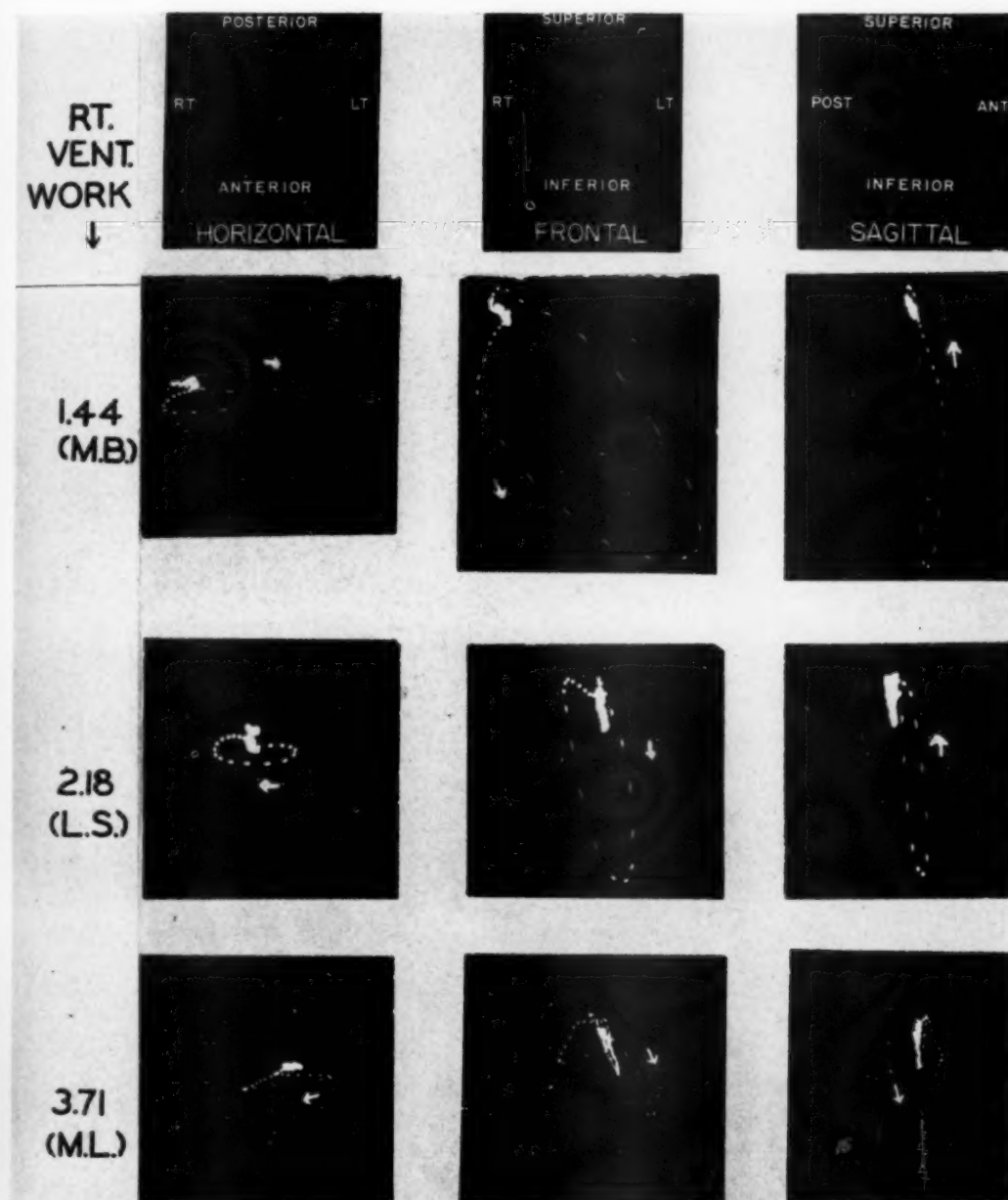M. A., with the greatest right ventricular work (3.03 units), forms more than

Fig. 1B.—Congenital heart disease.   See text.

one-half of the horizontal plane loop to the right of the E point, although the
spatial position of the QRS loop appears in the right, anterior, lower octant.
It is noted in Table III that there are more normal vectorcardiograms and electro-
cardiograms in patients with mitral stenosis than in those with congenital heart

disease, and this is further correlated with the almost equal distribution of patients with mitral stenosis having normal and abnormal right ventricular work levels.
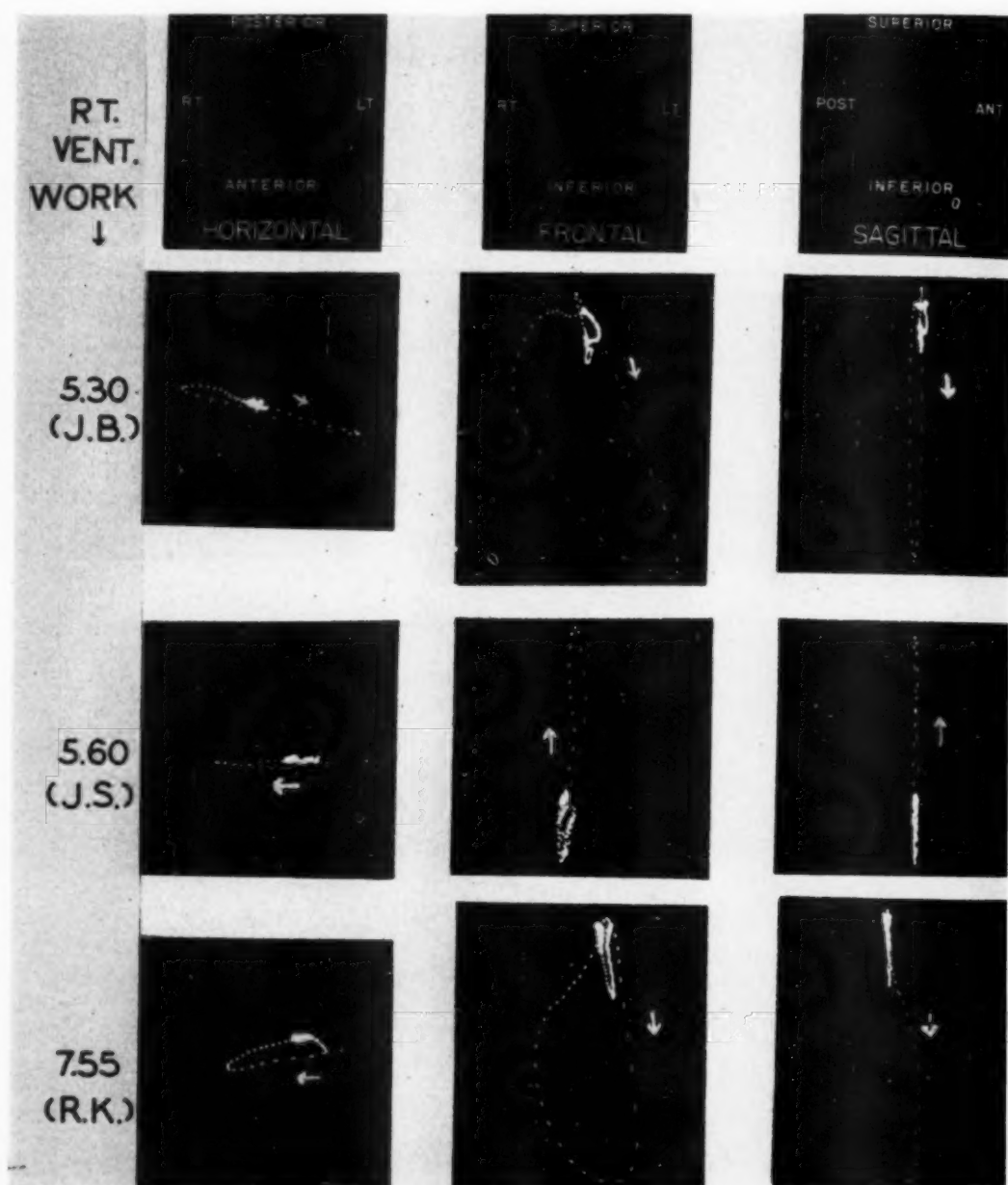

Fig. 1C.—Congenital heart disease. See text.

In "pure" right ventricular hypertrophy, in this series of patients, the vector-cardiogram may be used as a gross quantitative estimate of the degree of right ventricular hypertrophy which is important preoperatively.

TABLE III.   SUMMARY OF ELECTROCARDIOGRAPHIC AND VECTORCARDIOGRAPHIC DATA IN THE TWO LESIONS AND DIVIDED INTO NORMAL AND ABNORMAL RIGHT VENTRICULAR WORK

	RIGHT VENTRICULAR WORK UNITS*			
	GREATER THAN 1.06		LESS THAN 1.06	
Total number of patients	25		9	
Mitral stenosis	9		7	
Congenital heart disease	16		2	
	MITRAL STENOSIS	CONGENITAL HEART DISEASE	MITRAL STENOSIS	CONGENITAL HEART DISEASE
Normal vectorcardiogram	1	1	7	1
Vectorcardiogram of right ventricular hypertrophy	8	15	0	1
Normal electrocardiogram	2	1	7	2
Electrocardiogram of right ventricular hypertrophy	3	10	0	0
Electrocardiogram of incomplete right bundle branch block	4	5	0	0

*Units = kg. M./min./sq. M.

In congenital heart disease, (Table I), there were two patients, R. W. and J. P. (Fig. 1A), with right ventricular work less than 1.06 units. J. P. had a normal-sized heart by catheterization and orthocardiogram. The vectorcardiogram in all three planes was also normal; the QRS sÊ loop was in the posterior left lower octant. R. W. had an unusual vectorcardiogram. The horizontal loop formed a complicated double figure of eight (Fig. 1A) with a large portion of the loop inscribed to the right of E. The frontal loop was also a figure of eight, about one-half appearing inferiorly and to the left in sextant V and one-half superiorly and to the right in sextant II. The rotation was counterclockwise. The sagittal loop rotated clockwise (although direction was difficult to determine because of narrowness of the loop) and was located slightly posteriorly. The QRS sÊ loop was located slightly posteriorly, approximately midway between the right and left and the superior and inferior octants. Because of the spatial vectorcardiogram and despite the right ventricular work of 0.97 unit, this patient seems to represent comparatively early mild right ventricular hypertrophy. R. W. had pulmonary stenosis and interventricular septal defect and it may be that the pulmonary stenosis had not yet exerted its maximum hemodynamic effect. It is to be noted that both R. W. and J. P. had similar right ventricular work levels and electrocardiograms, but the vectorcardiograms were dissimilar.

Consideration of the spatial orientation of the QRS loops corroborates the observations of Lasser and associates[4] in increasing right ventricular hypertrophy.
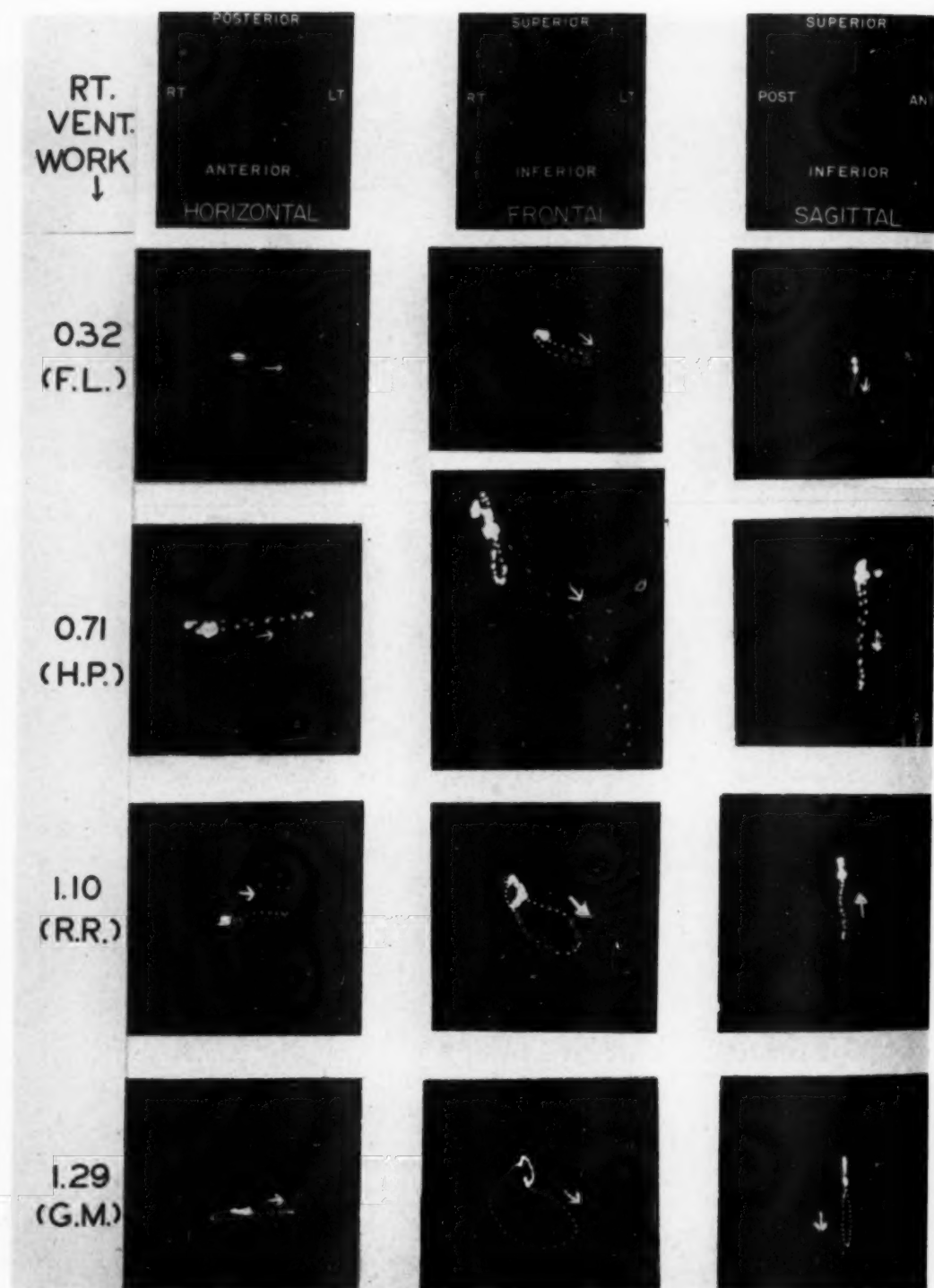
Fig. 2A.—Mitral stenosis arranged in order of increasing right ventricular work.   See text and Table II.
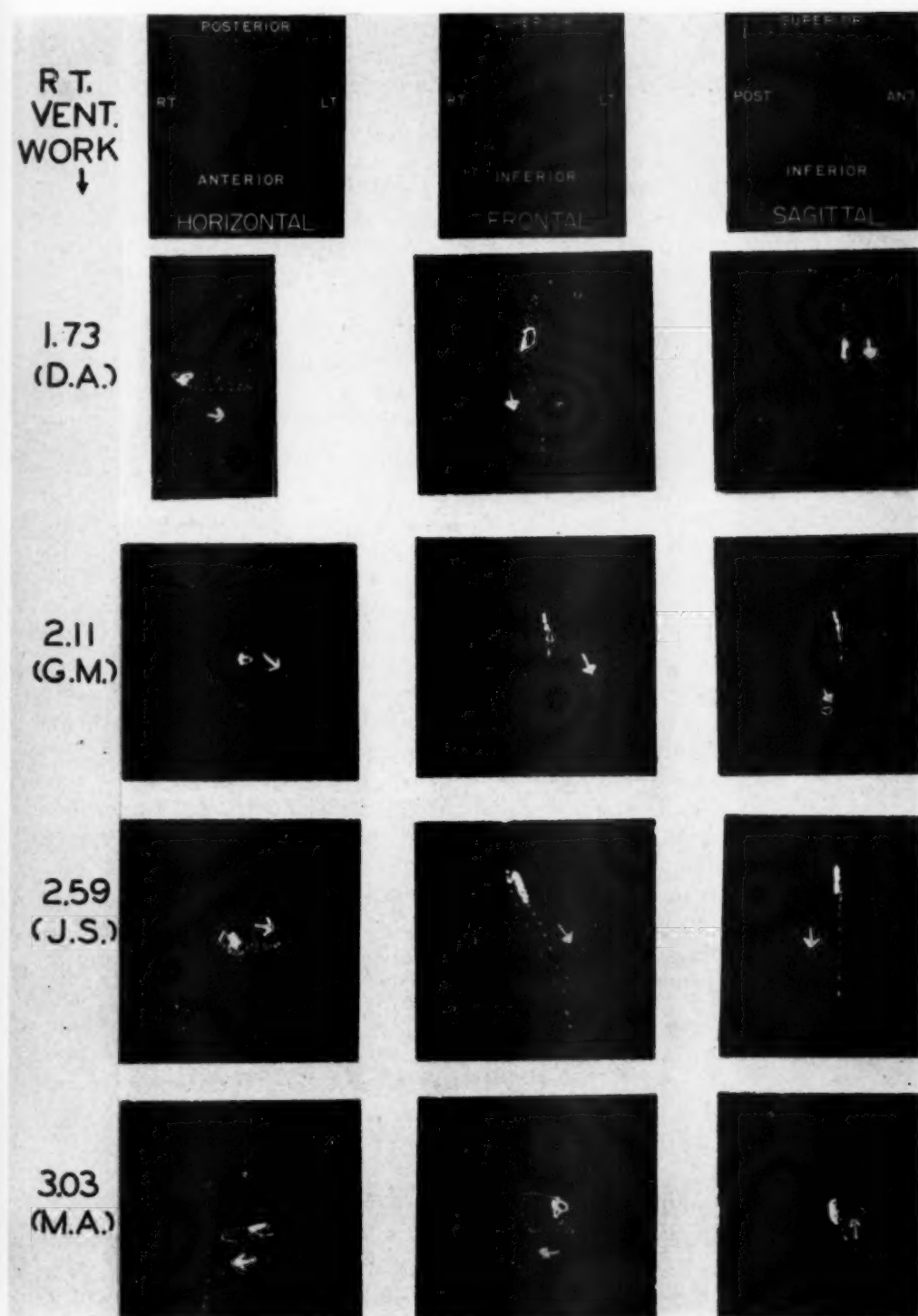
Fig. 2B.—Mitral stenosis. See text.

In contrast to their findings, none of our spatial QRS loops were in the right, posterior, upper octant. With increasing right ventricular work as seen in congenital heart disease, it is noted that the sagittal plane loop becomes counter-clockwise and more anterior in eight of the sixteen patients; this may be correlated with the more anterior position of the hypertrophied right ventricle.

One patient with congenital heart disease, M. C., (Table II) and one patient with mitral stenosis, D. A., (Table I) did not seem to fit the correlation between the vectorcardiogram and abnormal right ventricular work. M. C. had transposed pulmonary veins, with no cardiac symptoms, and the vectorcardiogram, electrocardiogram, and cardiac fluoroscopy were normal. The pulmonary artery pressure was at the upper limit of normal (30/12) and thus the considerable elevation of the right ventricular work was almost entirely due to the high pulmonary flow of ten liters per minute. In this unusual situation, it would seem that no appreciable right ventricular hypertrophy was demonstrable in spite of the apparent high ventricular work.

D. A. (Fig. 2B) with mitral stenosis had definite left auricular and right ventricular enlargement observed during cardiac surgery. After inserting the finger into the mitral valve, however, it was the surgeon's impression that this patient had greater mitral insufficiency than had been supposed. Therefore, it may be that there was more left ventricular hypertrophy than could be diagnosed clinically. Thus the balance of right and left cardiac hypertrophy may account for the absence of definite right ventricular hypertrophy in the vectorcardiogram. However, the loops showed abnormal pathways, especially in the horizontal plane; the loop had a terminal small appendage to the right of E with counter-clockwise direction. In the frontal plane, approximately one-third of the loop appeared in sextant II, and the sagittal loop was mostly anterior and rotated clockwise. Spatially, the loop was mostly oriented in the left anterior, lower octant, with extension to the right posterior superior octant. This type of vector-cardiogram[4] is obtained in patients with incomplete right bundle branch block in the electrocardiogram and was present in D.A.'s tracing. It is suspected that this vectorcardiogram may still represent right ventricular hypertrophy, the loops being modified by some degree of left ventricular hypertrophy.

R. R. (Fig. 2A) with a borderline right ventricular work (1.10 units) had a horizontal plane loop deviated to the left, anteriorly and clockwise. Although this may represent the earliest type of right ventricular hypertrophy, nevertheless no comparisons are available because this type has not been previously reported. J. B. (Fig. 1C) was unusual in that the electrocardiogram was interpreted as right ventricular hypertrophy and probably left ventricular hypertrophy; the QRS width was 0.11 to 0.12 second. The vectorcardiogram shows right ventricular hypertrophy and right bundle branch block and clarifies the interpretation of the electrocardiogram.

In twenty-two of the thirty-four cases, there was satisfactory correlation between the electrocardiogram and right ventricular work. In twenty-five patients with right ventricular work above normal (Table III), thirteen patients

had the classical pattern of right ventricular hypertrophy and three were normal; nine patients had incomplete right bundle branch block. Johnson and associates,[9] and Cosby and associates[10] have noted that incomplete right bundle branch block frequently occurs in association with right ventricular hypertrophy and elevated right ventricular work, but no decision has been made electrocardiographically[9,10] as to whether it is a conduction defect in the right bundle or a secondary result of right ventricular hypertrophy. This finding is also observed in normal hearts,[2,11] in acute cor pulmonale,[9] in coronary disease and in left ventricular hypertrophy.[12]   Lasser and associates[4,13] have demonstrated vectorcardiographically that this lesion may be due to right bundle branch block, abnormal pathway with normal conduction, or right ventricular hypertrophy, and that in six patients with congenital heart disease the vector loops of incomplete right bundle branch block were closely related to the vector loops seen in classical electrocardiographic patterns of right ventricular hypertrophy. Our nine patients with incomplete right bundle branch block, diagnosed as either congenital heart disease or mitral stenosis, showed right ventricular hypertrophy as judged by the vectorcardiogram and the elevated right ventricular work. This confirms the data of Lasser and co-workers[13] and extends them to patients with mitral stenosis as well.

In thirty-one of the thirty-four patients there was good correlation between the vectorcardiogram and right ventricular work (Tables I and II).   The three exceptions, M.C., R.W., and D.A., have been discussed above. Of the twenty-five patients with abnormal right ventricular work, twenty-three had right ventricular hypertrophy and two were normal. Table III illustrates that the spatial vectorcardiogram has a closer relationship to right ventricular hypertrophy and work than does the electrocardiogram.

SUMMARY

1.   A vectorcardiographic study of thirty-four patients with congenital heart disease and mitral stenosis is reported.   All patients had cardiac catheterization and none except one had left ventricular hypertrophy.

2.   With increasing right ventricular work, there is an increased rightward and anterior deviation of the horizontal plane loop and of the spatial vectorcardiogram to the right anterior inferior octant in both lesions.

3.   There is a better correlation between the vectorcardiogram and right ventricular work than between the electrocardiogram and right ventricular work.

4.   The vectorcardiogram shows the pattern of right ventricular hypertrophy clearly.   The electrocardiogram is usually reliable only in the classical pattern of right ventricular hypertrophy but not when incomplete right bundle branch block is present.   In nine patients with incomplete right bundle branch block, the vectorcardiogram clearly shows that this lesion also represents right ventricular hypertrophy, thus confirming previous studies in congenital heart disease and extending them to patients with mitral stenosis as well.

5.   The vectorcardiogram may serve as a gross quantitative estimate of the degree of right ventricular hypertrophy, especially in congenital heart disease.

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LEFT BUNDLE BRANCH BLOCK MASQUERADING AS RIGHT BUNDLE BRANCH BLOCK

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D URING the study of spatial vectorcardiography, four vectorcardiograms were encountered which displayed the signs of left bundle branch block. The electrocardiograms, however, were diagnostic of right bundle branch block, according to the generally accepted criteria of Wilson.[1] According to these criteria, right bundle branch block is assumed to be present when the right-sided precordial leads display late R or R' deflections, regardless of the morphology of the limb leads. That is, the precordial leads are considered more reliable than the limb leads in determining the site of block. Although the precordial leads in our cases were characteristic of right bundle branch block, the limb leads were suggestive of left bundle branch block. Tracings of this sort have been reported by others and considered examples of right bundle branch block.[2-5] The apparent paradox has been attributed to a vertical heart position or myocardial infarction. The four cases herein reported belong in this group, but our understanding of them differs from the conventional concept.

METHOD

The vectorcardiographic method used in this laboratory is described in detail elsewhere.[6] A modification of the orthogonal reference system of Duchosal is employed. No more exertion on the part of the patient is required than in the taking of an electrocardiogram. Three mutually perpendicular planes, horizontal, sagittal, and coronal or frontal, are recorded, successively. The polarity is positive, i.e., vectors are directed from active to resting muscle, or from endocardium to epicardium. Intensity modulation at a rate of 400 cycles per second serves as a timing device; close spacing of the interruptions indicates slow change and wide spacing rapid change of direction and magnitude of the vectors.

CASE REPORTS

CASE 1.—C. B., a 71-year-old man, was admitted to the hospital for the fifth time on Nov. 1, 1951, for intermittent chest pain of five days' duration. Diagnoses in previous admissions were acute myocardial infarction, digitalis intoxication, and bleeding duodenal ulcer. Examination revealed a temperature of 99.4°, blood pressure 120/58 mm. Hg, cardiomegaly, and distant heart sounds. The white blood count was 11,150, and the corrected sedimentation rate was 37 mm. per hour. A diagnosis of acute myocardial infarction was made. The hospital course was uneventful, and the patient was discharged improved on Nov. 22, 1951.

Electrocardiograms.—Electrocardiograms taken during the first admission in 1950 disclosed complete left bundle branch block, and first degree atrioventricular block (Fig. 1A). Subsequent electrocardiograms remained unchanged until November, 1951 when the following changes were noted: qR deflections in Lead I, wide slurred R and inverted T waves in Lead aV$_R$, M-shaped QRS complexes and inverted T waves in the right-sided precordial leads, and qR deflections and
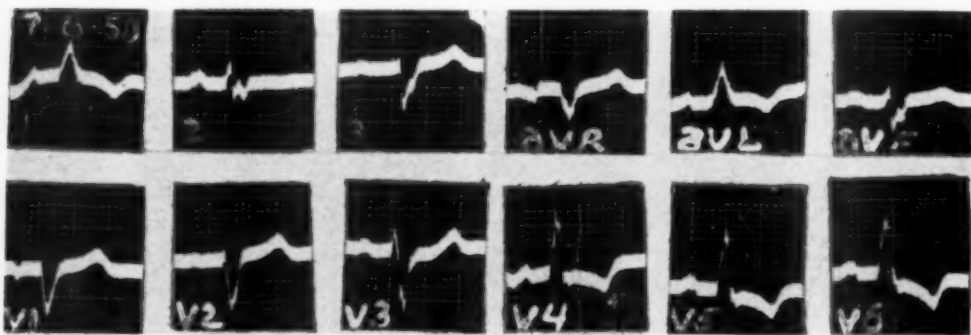

Fig. 1A (Case 1).—Electrocardiogram taken July 6, 1950. P-R interval, 0.21 sec. QRS interval 0.13 sec. Left bundle branch block.
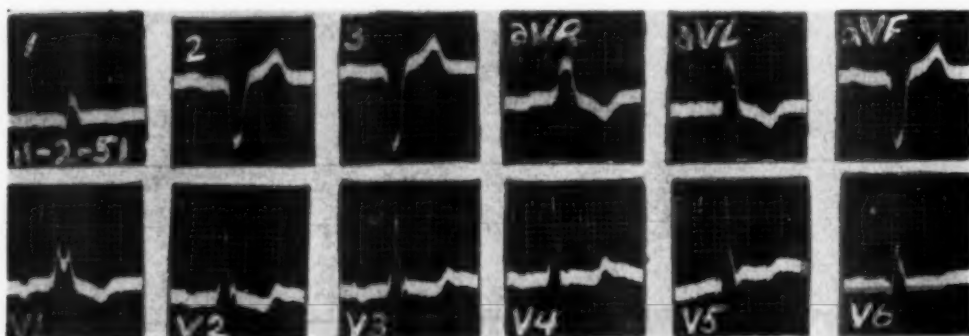
Fig. 1B (Case 1).—Electrocardiogram taken Nov. 2, 1951. P-R interval, 0.24 sec. QRS interval, 0.15 sec. Note changes in Leads I, aV$_R$ and precordial leads. The initial negativity in the superior Leads aV$_R$ and aV$_L$ and the initial postivity in aV$_F$ are not readily apparent because of the minute size of the initial inferiorly directed QRS vectors. See text.

Fig. 1C (Case 1).—Electrocardiogram taken June 11, 1952. Similar to Fig. 1B except for further changes in the precordial leads. See Fig. 2 and text.

inverted T waves in Leads V₅ and V₆ (Fig. 1B).   Later tracings displayed notched QS deflections and upright T waves in Leads V₅ and V₆ (Fig. 1C).   First degree atrioventricular block was present in all tracings.

Spatial Vectorcardiograms.—Spatial vectorcardiograms obtained in November, 1951 and subsequently in June, 1952 (Fig. 2) were identical.   The initial QRS forces point slightly anteriorly and inferiorly but do not deviate laterally.   The succeeding QRS vectors change direction abruptly to a superior, anterior, and rightward position, attaining considerable magnitude in the superior direction.   The late QRS vectors display a superior, posterior, and rightward orientation.   The centripetal limb of the QRS loop, composed of these late QRS vectors, is slowly inscribed and approaches but does not reach, the starting or 0 point, resulting in an "open" QRS loop.   The QRSsÊ loop describes an irregular course.   The T loop is separated from the QRS loop by 180°.

Fig. 2 (Case 1).—Spatial vectorcardiogram taken June 11, 1952. In this and the following vector-cardiograms the projections are: *H* = Horizontal; *S* = Sagittal; and *F* = Frontal or Coronal.   The large interrupted loop in each projection is the QRS loop and the smaller heavier loop, the T loop.   The arrow indicates the direction of inscription of the QRS loop.   The initial QRS vectors are directed inferiorly and anteriorly and are small.   Note the irregularity, and the terminal slow inscription of the QRS loop.   Direction of inscription of the sagittal and coronal loops is unusual.

CASE 2.—I. F. a 66-year-old man was admitted to the hospital for the first time on June 25, 1952, following an attack of chest pain which lasted thirty minutes.   There was a history of diabetes for twelve years, angina pectoris for five years, and two episodes of acute myocardial infarction, two and one-half, and one year previously.   Congestive heart failure had been present for one year.   Examination revealed a temperature of 99.6°, blood pressure 120/80 mm. Hg, cardiomegaly, slow irregular heart action, a Grade 2 apical systolic murmur, distended neck veins, basal pulmonary râles, hepatomegaly and pitting sacral and ankle edema.   The white blood count was 6,950 and the corrected sedimentation rate 37 mm. per hour.   A diagnosis of coronary heart disease and congestive heart failure was made.   The course was uneventful and the patient was discharged improved on July 12, 1952.

· *Electrocardiograms.*—Electrocardiograms revealed a QRS interval of 0.15 sec.; left-axis deviation; qRs complexes and upright T waves in Leads I and aV_L; small q, tall, wide, notched R waves and inverted T waves in Leads aV_R, V₁ and V₂; q, tall notched R, and late wide and notched S waves in V₃, V₄, and V₅; and notched QS deflections and upright T waves in Lead V₆.   First degree atrioventricular block was present on all tracings except one which displayed transient high grade atrioventricular block (Fig. 3).

Spatial Vectorcardiograms.—Spatial vectorcardiograms taken before and during this ad-mission were identical.   The initial QRS vectors are directed anteriorly, inferiorly, and to the left.   The succeeding QRS vectors change direction abruptly to an anterior, superior, and rightward position, attaining considerable magnitude superiorly.   The late QRS vectors are oriented superiorly and to the right and diminish in magnitude; except for the anterior projection of a secondary loop, there is no anteroposterior displacement.   The centripetal limb of the QRS loop, composed of these late QRS vectors, slowly approaches but does not reach the 0 point, resulting in an "open" loop.   The QRSsÊ loop describes an irregular course.   The T loop is separated from the QRS loop by 180° (Fig. 4).
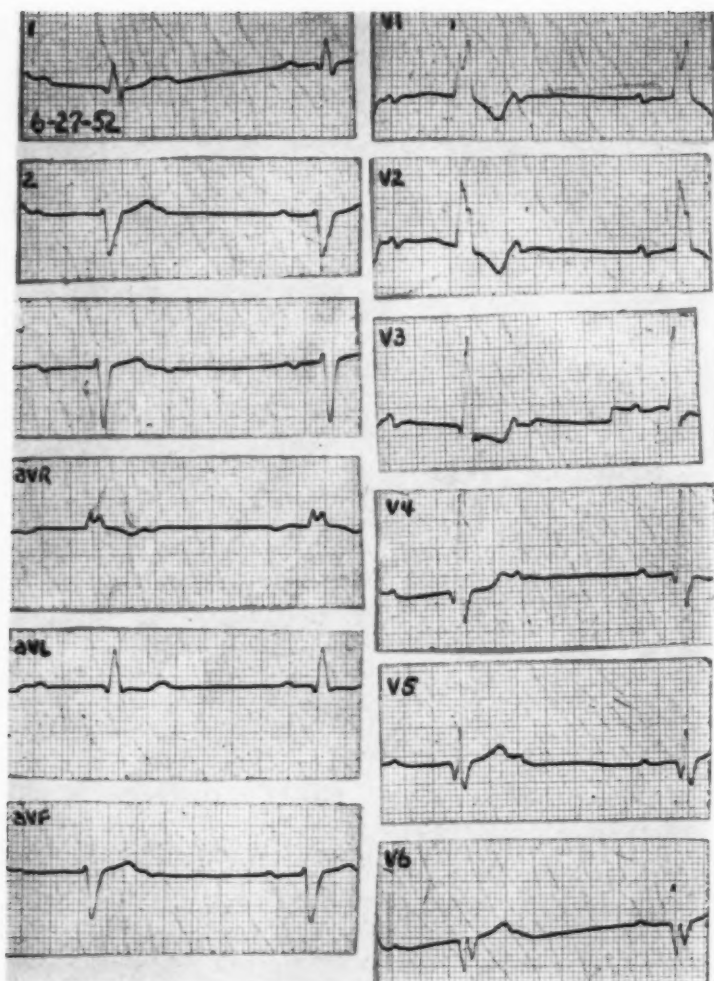
Fig. 3 (Case 2).—Electrocardiogram taken June 27, 1952. Complete atrioventricular dissociation. QRS interval, 0.15 sec. Unlike the other three cases there are S waves in Leads I and aV$_L$, and the resemblance to left bundle branch block is less striking. QRS-T complexes similar to those present before and after atrioventricular block occurred.

Fig. 4 (Case 2).—Spatial vectorcardiogram taken June 27, 1952. The initial QRS vectors are directed anteriorly, inferiorly, and to the left. Except for the anterior projection of a secondary loop, the late QRS vectors have no anterior-posterior deviation.

CASE 3.—H. C., a 54-year-old man, entered the hospital for the first time on June 25, 1952, five days following an attack of severe prolonged chest pain.   An electrocardiogram obtained at the onset disclosed complete heart block and aberrant ventricular complexes.   The patient had had angina pectoris for five years and a cerebral accident one year previously.   Examination revealed a temperature of 100.2°, blood pressure 100/70 mm. Hg, and basal pulmonary râles.   White blood count was 15,100, and corrected sedimentation rate was 37 mm. per hour.

A diagnosis of acute myocardial infarction and acute pulmonary embolism was made.   On the day of admission a right hemiparesis occurred, which gradually subsided.   On the seventh day pleuritic chest pain and hemoptysis occurred.   Three days later the signs of acute congestive failure appeared, and digitoxin and mercurial diuretics were administered.   On the thirtieth hospital day the patient was transferred to another institution for prolonged hospital care.
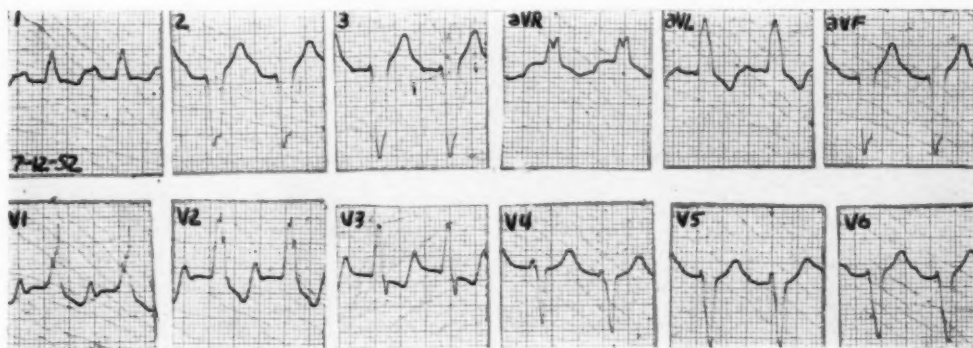
Fig. 5 (Case 3).—Electrocardiogram taken July 12, 1952.   P-R interval prolonged and variable, with two periods of transient high-grade atrioventricular block.   QRS interval, 0.18 sec.   See text.
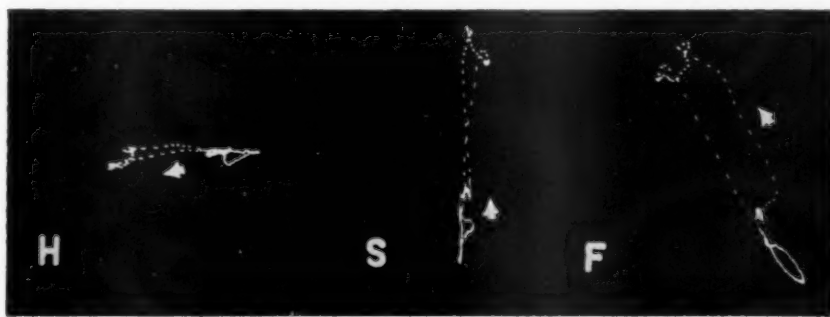
Fig. 6 (Case 3).—Spatial vectorcardiogram taken July 12, 1952.   The initial vectors point anteriorly, inferiorly, and to the left; the P loop obscures the initial vectors in the H and S projections. The late QRS vectors have no significant anterior-posterior projection but are posteriorly directed terminally.   See text.

Electrocardiograms.—Electrocardiograms on admission showed a normal sinoauricular rhythm with prolongation of the P-R interval and a QRS interval of 0.18 sec.; left-axis deviation; small q waves, slurred and notched R and inverted T waves in Leads I and aV_L; M shaped QRS complexes and inverted T waves in Lead aV_R and the right-sided precordial leads; and rS deflections and upright T waves in Leads aV_F and V_4 to V_6 (Fig. 5).   Transient complete heart block recurred on the seventh hospital day.

Spatial Vectorcardiograms.—Spatial vectorcardiograms were obtained on the eighteenth hospital day.   The initial QRS vectors are directed anteriorly, inferiorly, and to the left.   The succeeding QRS vectors change direction abruptly to a superior, anterior, and rightward position, attaining considerable magnitude superiorly.   After attaining maximum magnitude in this

direction, the QRS vectors decrease and become posteriorly oriented; the centripetal limb of the QRS loop returns toward but does not reach the 0 point, resulting in an "open" QRS loop. The QRSsĒ loop describes an irregular course. The T loop is separated from the QRS loop by 180° (Fig. 6).

CASE 4.—J. S. a 94-year-old man, was admitted to the hospital for the second time on Sept. 21, 1952, for severe chest pain followed by unconsciousness, five hours before admission. The patient appeared moribund, the blood pressure was 170/110 mm. Hg, the heart rhythm was irregular at a rate of 44, and there was a Grade 2 apical systolic murmur. White blood count was 10,900 and corrected sedimentation rate was 14 mm. per hour, rising to 32 mm. per hour on the sixth hospital day. Except for a period of faintness associated with tachycardia on the fifteenth hospital day, the course was uneventful, and the patient was discharged improved on Oct. 19, 1952.
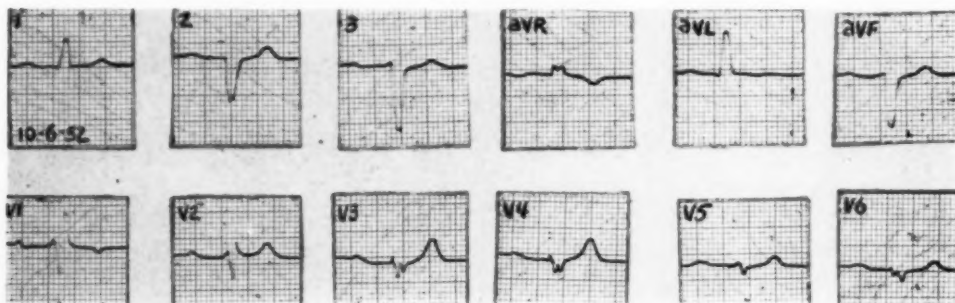

Fig. 7 (Case 4).—Electrocardiogram taken Oct. 6, 1952. P-R interval 0.28 sec. QRS interval 0.14 sec. Q waves in aV$_R$ and the initial R waves in aV$_F$ are very small. See text.
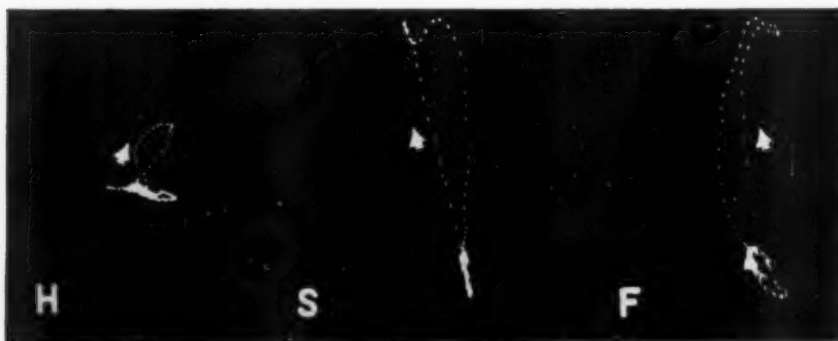

Fig. 8 (Case 4).—Spatial vectorcardiogram taken Oct. 6, 1952. The initial QRS vectors, obscured by the T loop in the H and S projections, are directed anteriorly, inferiorly, and to the left. Largest QRS vectors are directed more posteriorly and less to the right than in other cases but otherwise the vectorcardiograms are similar. See text.

Electrocardiograms.—Electrocardiograms displayed high grade atrioventricular block in the first tracing, and first degree atrioventricular block subsequently. The QRS interval was 0.14 sec. There were: left axis deviation; qR complexes and upright or diphasic T waves in Leads I and aV$_L$; qR deflections and inverted T waves in aV$_R$; rSR' deflections in the right-sided precordial leads; and RS deflections and upright T waves in Lead aV$_F$ and the left-sided precordial leads (Fig. 7).

Spatial Vectorcardiograms.—Vectorcardiograms taken on the fifteenth hospital day showed initial QRS vectors directed anteriorly, inferiorly, and to the left. The succeeding QRS forces change direction abruptly to point posteriorly, superiorly, and slightly to the right, attaining considerable magnitude in the superior and posterior direction. The late QRS vectors are directed posteriorly, superiorly, and to the right. The centripetal limb of the QRS loop approaches but does not reach

the 0 point, resulting in an "open" QRS loop. The QRSsÊ loop describes an irregular course. The T loop is separated from the QRS loop by about 180° (Fig. 8).

SUMMARY OF ELECTROCARDIOGRAPHIC AND VECTORCARDIOGRAPHIC OBSERVATIONS

The electrocardiograms have the following features: (1) wide QRS interval; (2) left-axis deviation; (3) qR deflections in Leads I and aV_L; (4) qR or R deflections in Lead aV_R; (5) rS deflections in Lead aV_F; (6) slurred or notched R waves in the right-sided precordial leads; (7) rS or notched QS deflections in the left-sided precordial leads; and (8) atrioventricular block.

The vectorcardiograms have the following features: (1) the initial QRS forces are small and point anteriorly and inferiorly with or without leftward deviation; (2) the subsequent QRS forces point superiorly and to the right and either anteriorly or posteriorly; (3) the terminal QRS vectors point superiorly, posteriorly, and to the right; (4) the QRSsÊ loop displays an irregular course; (5) the terminal portion of the QRSsÊ loop is slowly inscribed; and (6) the T vectors are directed opposite to the QRS vectors.
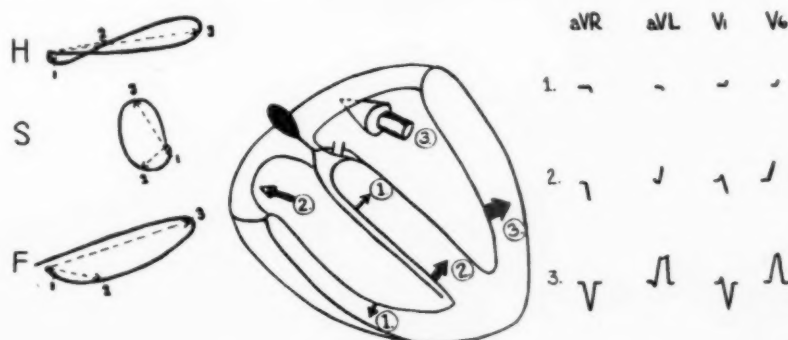

Fig. 9.—Schematic section of heart and representation of ventricular depolarization in uncomplicated left bundle branch block. The arrows represent component vectors contributed by specific areas of myocardium; the numbers indicate the order of depolarization. In the vectorcardiogram on the left the arrows are representative resultants of the component vectors seen in the section of the heart. The electrocardiographic leads (aV_R, aV_L, V_1 and V_6) to the right depict the QRS complexes at three instants during ventricular systole, corresponding to the numerals seen in the section of the heart. See text.

DISCUSSION

A force having magnitude, direction, and sense can be represented as a vector. At each instant during cardiac activity, all electrical forces are summated into one manifest force or resultant vector having these properties. This manifest force or resultant vector is called the "cardiac vector". A proper understanding of left bundle branch block is dependent on a knowledge of the cardiac vector and of the factors that change it at each instant during cardiac activity.[6]

The characteristic vectorcardiographic and electrocardiographic patterns observed in uncomplicated left bundle branch block are determined by the order of depolarization of the ventricular mass[7,8] (Fig. 9). The first fractions of myocardium to be depolarized·are the septum in a right-to-left direction, and the free right ventricular wall, resulting in initial QRS vectors directed inferiorly, slightly

anteriorly, and to the left. This is reflected in the electrocardiogram by initial negative deflections in the superior leads, aV_R and aV_L and initial positive deflections in the inferior Leads V_E and aV_F and the left-sided precordial leads. The right-sided precordial leads may or may not have initial positive deflections. The subsequent forces are predominantly those arising in the thick septum; the corresponding resultant vectors are directed posteriorly, superiorly, and to the left. These vectors result in positive deflections in Lead aV_L and the left-sided precordial leads and negative deflections in Lead aV_R and the right-sided precordial leads. The belated depolarization of the free wall of the left ventricle introduces new and powerful forces at a time when the septal forces are declining or are insignificant, and the QRS vectors continue their leftward and superior direction until the left ventricular forces wane and are finally extinguished. Coincident with the decline of these forces the late positive deflections in the left-sided leads and the late negative deflections in the right-sided leads return toward the isoelectric level and cross it. S-T segment displacement occurs because the prolonged depolarization interval permits sufficient growth of the recovery forces to be recorded and is represented in the vectorcardiogram by an open QRS loop. The T loop is separated from the QRS loop by 180°.

The initial QRS vectors are the most characteristic feature of left bundle branch block[6] and are constant, even in the presence of complicating factors, such as myocardial infarction. The initial vectors in the cases here described are identical with those seen in uncomplicated left bundle branch block observed by us.[6] Although the subsequent QRS vectors appear to resemble the late QRS vectors of right bundle branch block, the initial forces preclude this possibility and warrant the diagnosis of left bundle branch block. Furthermore, despite the superficial resemblance of the terminal forces in our four cases to those seen in right bundle branch block, important differences are present. The late rightward QRS forces in right bundle branch block are directed anteriorly and are small in comparison with the earlier leftward forces.[6,9] These features contrast strikingly with those observed in the cases under discussion; the rightward forces are not anteriorly oriented, and they greatly exceed in magnitude the small initial and early forces directed to the left.

Nevertheless, except for the initial vectors, these vectorcardiograms differ markedly from those seen in left bundle branch block, and this fact must be explained. The early QRS vectors, which are usually dominated by septal forces, do not point posteriorly, superiorly, and to the left, but anteriorly, superiorly, and to the right. This change in vector direction is explained by assuming extensive septal infarction so that the new resultant vectors are dominated by the now largely unopposed right ventricular potentials. These early abnormal vectors account for the R wave in the right-sided precordial leads, and the early negative deflections in the left-sided precordial leads; their superior direction gives rise to the early R waves in Leads aV_R and aV_L. With the introduction, belatedly, of forces arising in the free left ventricular wall, a change in direction of the resultant vectors takes place; they point to the right, posteriorly, and markedly superiorly. This contrasts with the anticipated leftward orientation of the terminal vectors in left bundle branch block and suggests that forces which normally arise in the lateral and diaphragmatic walls of the left ventricle are

absent.   The abnormal terminal forces are reflected in the late positive deflections in the superior leads, aV_R and aV_L, and the right-sided precordial leads, and the late negative deflection in the left-sided precordial leads (Fig. 10).

Left bundle branch block usually precludes the development of the QRS abnormalities which are diagnostic of myocardial infarction.[4]   Exceptions have been reported by Wilson and associates,[2] Sodi-Pallares and associates,[10] Osher and Wolff,[11] and others, in cases with considerable septal infarction.   In all probability, QRS changes always occur when there is infarction of the free wall of the left ventricle even when the septum is spared.   RS deflections in the left-sided precordial leads in the presence of transmural infarcts have been described,[2,10] but since such ventricular complexes occur in uncomplicated left bundle branch block, they cannot be considered diagnostically significant.
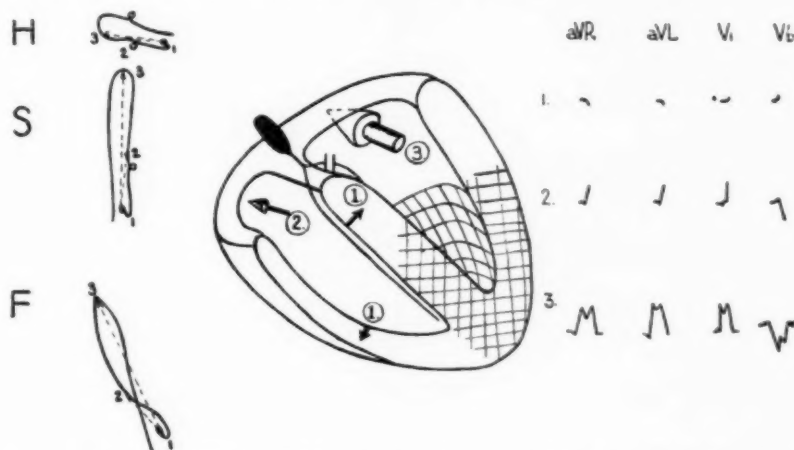

Fig. 10.—Similar to Fig. 9.   Left bundle branch block complicated by myocardial infarction.   Cross-hatched areas represent myocardial infarction.   See text.

The conventional explanation of the QRS changes which occur in myocardial infarction complicated by left bundle branch block is based on the concept of an "electrical window."[2]   According to this concept infarcted tissue behaves as a transparent pathway which transmits cavity potentials from one side of the heart to the other and to epicardial surface.   However, the mechanism responsible for the·QRS changes which follow myocardial infarction is no different, fundamentally, whether left bundle branch block or normal intraventricular conduction is present.   Electrodes placed on the endocardial and epicardial surfaces of the normal left ventricular wall have different spatial orientations to the over-all electrical field of the heart because of the presence, between the electrodes, of excitable tissue.   Therefore, the potentials are different in these areas.   On the other hand, electrodes placed on the endocardial and epicardial surfaces of a transmural infarct subtend practically identical angles with the over-all forces arising in the heart because excitable tissue is no longer present between the electrodes.   Such electrodes, therefore, record essentially identical potentials.   In other words, under these circumstances, the cavity and epicardial potentials are the same because cavity leads are no different in their derivations than are other leads.[12]   The disappearance of forces consequent to myocardial infarction

alters the entire electrical field surrounding the heart and a new balance of forces, directed away from the infarcted area, is created.   Accordingly, all leads, be they endocardial (cavity), or epicardial (precordial) will reflect the change.   The changes in the QRS complex in myocardial infarction, therefore, are due solely to the altered electrical field consequent to the removal of excitable tissue.   In the presence of left bundle branch block, a unique situation exists, because depolarization of the septum and of the free left ventricular wall is separated by an abnormally long interval.   Therefore, septal infarction results in a change early, and free wall infarction results in a change late in the depolarization period.

CONCLUSIONS

Vectorcardiographic study of these four cases has clarified a paradox occasionally seen, namely, electrocardiograms in which the limb leads resemble left bundle branch block and the precordial leads resemble right bundle branch block.   These have been interpreted in the past as examples of right bundle branch block, modified by infarction or unusual heart position.   Our observations indicate that these electrocardiograms represent left bundle branch block. Evidently, whereas Wilson's criteria for the localization of bundle branch block are true in most cases, the limb leads in these cases are a more reliable indicator of the type of block than are the precordial leads.   Furthermore, we conclude from these studies that the vectorcardiogram reveals evidence of myocardial infarction, in the presence of left bundle branch block, and that the same is true for the electrocardiogram if properly interpreted.   These studies suggest that tracings which have the paradoxical features mentioned should be regarded as examples of left bundle branch block modified by extensive septal and posterolateral myocardial infarction.

SUMMARY

1.   Four cases having electrocardiograms with the following features have been presented: (a) signs of left bundle branch block in the limb leads; (b) signs of right bundle branch block in the precordial leads; (c) qR deflections in aV_R.

2.   Vectorcardiograms were obtained in these cases, all of which reveal the nature of the conduction defect to be left bundle branch block.

3.   The mechanisms responsible for the unusual vectorcardiographic and electrocardiographic features have been discussed.

4.   These observations suggest that electrocardiograms showing the paradoxical features described be interpreted as left bundle branch block with extensive septal and inferolateral myocardial infarction.

5.   As might be expected in posterior infarction, high grade atrioventricular block is an occasional feature.

ADDENDUM

After this paper was written the electrocardiogram reproduced in Fig. 11 came to our attention. It displays the signs of right bundle branch block in the precordial leads and left bundle branch block in the limb leads and is similar to those described. Post-mortem examination revealed extensive myocardial infarction involving the interventricular septum and the posterolateral wall of the left ventricle, supporting our interpretation of the electrocardiograms in this group.   If

the conduction defect exhibited in the electrocardiogram were right, and not left bundle branch block, the infarct should have involved the anterolateral wall of the left ventricle, and the septum should have been spared.
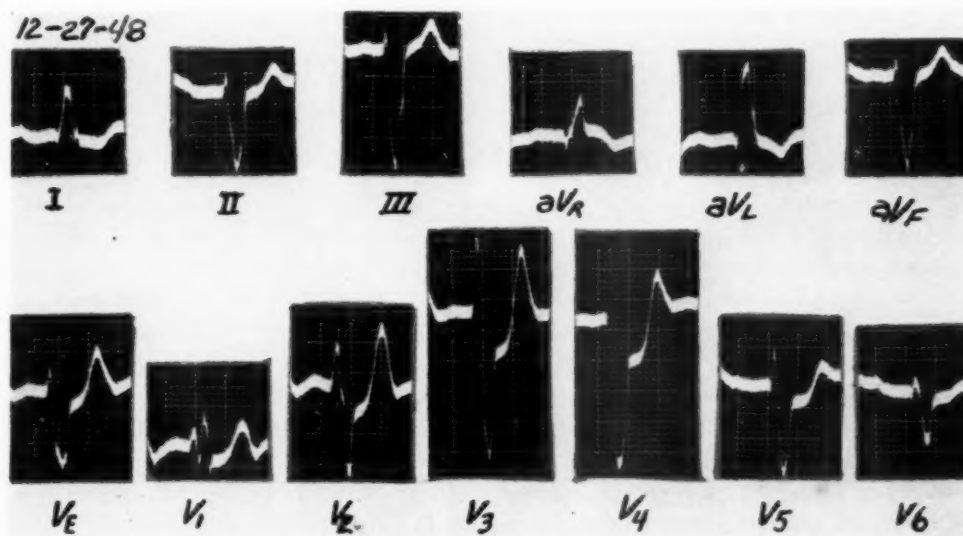

Fig. 11.—Electrocardiogram of S. J. P-R interval, 0.24 sec. QRS interval, 0.16 sec. Note the features of left bundle branch block in the limb leads and right bundle branch block in the precordial leads and the qR in Lead aV_R. Marked S-T segment depressions are present in the precordial leads. See Addendum to text.

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EFFECT OF COOLING THE ANTERIOR CHEST WALL ON THE T WAVE OF THE ELECTROCARDIOGRAM

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THAT cooling or warming the heart surface has an effect on the electrocardiogram was shown by Bayliss and Starling in 1892.[1] Subsequent experiments have confirmed this observation. In 1923, Wilson and Finch[2] noticed that ingestion of cold water increased the negativity of the T wave in Leads II and III.

Recently, Dowling and Hellerstein[3] have repeated the experiments of Wilson and Finch and noticed the effect of ingestion of cold water on the T wave of the electrocardiogram using the unipolar limb leads and the multiple precordial leads. They noticed that ingestion of 800 c.c. of iced water gave rise to primary T-wave changes which lasted for about twenty-five minutes, the maximum changes occurring within five minutes following ingestion of iced water. Their experiments supported the concept that the T-wave changes observed were due to the delayed repolarization of the posteroinferior surface of the left ventricle in contact with the distended fundus of the stomach. The T-wave changes after drinking iced water may, presumably, be due to the actual cooling of the epicardial surface of the heart through the stomach and the diaphragm. The present investigators thought it worth while to see if the cooling of the anterior surface of the chest wall would act in the same way, i.e., it would cool that part of the anterior region of the heart which is in contact with the anterior chest wall and thus give rise to primary T-wave changes. This work may, therefore, be considered as a corollary to that done by Wilson and Finch[2] and by Dowling and Hellerstein.[3]

MATERIAL AND METHOD

The subjects selected were all apparently healthy men, most of them working as attendants or technicians in the laboratories of the Department of Physiology of the Osmania Medical College. A few students of the physiology class of the Medical College were also included. The age of the subjects varied from 19 years to 60 years (Table I).

The experiments were done either in the morning or in the afternoon at least two hours after the subject had partaken of any meal. The subject lay supine with the head resting on a small pillow for about fifteen minutes before the control electrocardiographic records were taken. The machine used was a Sanborn Viso-Cardiette. Leads I, II, III, aV_R, aV_L, aV_F, V_1 through V_4, V_6, and V_8 were taken and the blood pressure was also recorded. An ice bag about nine inches in diameter containing pounded ice was then kept on the chest in the

TABLE I

SUBJECT NO.	AGE (YR.)	WEIGHT (KG.)	SITTING HEIGHT (CM.)	PELIDISI	BLOOD PRESSURE, MM. HG				PULSE RATE ALTERATION (%)
					BEFORE COOLING		AFTER COOLING		
					SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	
1	40	33.8	83.0	83.9	104	68	110	72	nil
2	35	57.1	84.0	98.9	110	70	110	70	nil
3	45	49.4	88.0	89.7	108	75	108	80	−7
4	25	44.4	86.0	86.4	95	65	95	70	+12
5	28	54.3	86.5	94.3	115	65	115	70	+12
6	60	41.2	81.5	91.3	98	65	128	75	−3
7	32	49.4	83.5	94.5	102	72	120	80	+7
8	26	56.0	87.0	94.7	110	75	110	75	nil
9	38	54.0	81.5	99.9	105	75	110	80	+2
10	36	59.5	87.5	96.1	115	80	122	85	+6
11	23	46.2	87.5	88.3	100	75	100	75	−7
12	20	52.0	86.0	93.2	100	70	100	70	nil
13	24	49.7	86.0	92.1	110	75	115	80	−4
14	19	50.7	89.5	87.9	100	75	105	80	+8
15	21	66.4	92.0	94.8	110	75	110	75	nil
16	21	48.2	91.0	86.1	105	65	105	65	nil

precordial region. After the bag had remained for five minutes, the electrocardiographic records from the limb leads, both standard and unipolar, were obtained with the bag still in position. The bag was then removed from the chest, and the precordial leads were obtained. By this time the bag had remained on the chest for about six minutes. Care was taken that the chest electrode was placed on the precordium at exactly the same position as when the control records were taken.

All the experiments were performed during the months of June and July, 1953, when the room temperature was about 30°C. The placing of the ice bag did not give rise to any acute or unbearable distress in these subjects. In subjects 2 and 7, who did not show marked T-wave changes, the experiment was repeated on another day using an ice and salt mixture in the bag which lowered the temperature to about −6°C. More marked T-wave changes were then obtained.

The ventricular gradient was measured by the method given by Wilson and associates[4] and by Ashman and Byer.[5] A hand lens was used for measuring the areas of QRS and T. The areas were measured in Leads I and III, and the result checked with the areas obtained in Lead II. The measurements were taken by at least two of us independently and, whenever necessary, the results were rechecked and adjustments made. In this way it was possible to minimize the large margin of error in personal judgment in the measurement of the areas. We believe that the results thus obtained on the basis of these measurements gave a fairly accurate idea of the changes taking place in the potential and the axis of $\hat{A}_{QRS}$ and $\hat{G}$. The magnitude and the axis of $\hat{A}_{QRS}$ and $\hat{G}$ were obtained by the use of Einthoven's triangle.

RESULTS

The cooling of the precordial region of the chest wall gave rise to depression (decreased positivity or increased negativity) of the T wave in Leads V_1 to V_4 (Figs. 1 and 2). The degree of change in the T-wave amplitude was not of the same order in all subjects. It was noticed that the change was less marked in subjects in better state of nutrition and with a thicker chest wall than in subjects in a poorer state of nutrition and with a thinner chest wall. Table I gives the pelidisi of the subjects investigated. Pelidisi is the relationship between the weight of the individual and his sitting height. This method of fixing the state of nutrition of the individual was first originated by the late Professor Clement Pirquet[6] of Vienna and is known as the Pirquet index. It is expressed by the formula,

$$\frac{\sqrt[3]{10 \times \text{weight in grams}}}{\text{Sitting height in centimeters}}$$

and the result is multiplied by 100.

A pelidisi of 97 or 98 has been found to represent a normal state of nutrition in the adult in the western countries. It has been stated that in these adults a pelidisi around 90 represents a distinctly low state of nutrition and that a pelidisi of over 100 represents a fat person. In a previous investigation, one of us[7] found that the average pelidisi of a group of young male subjects at Hyderabad was 92 ± 4.

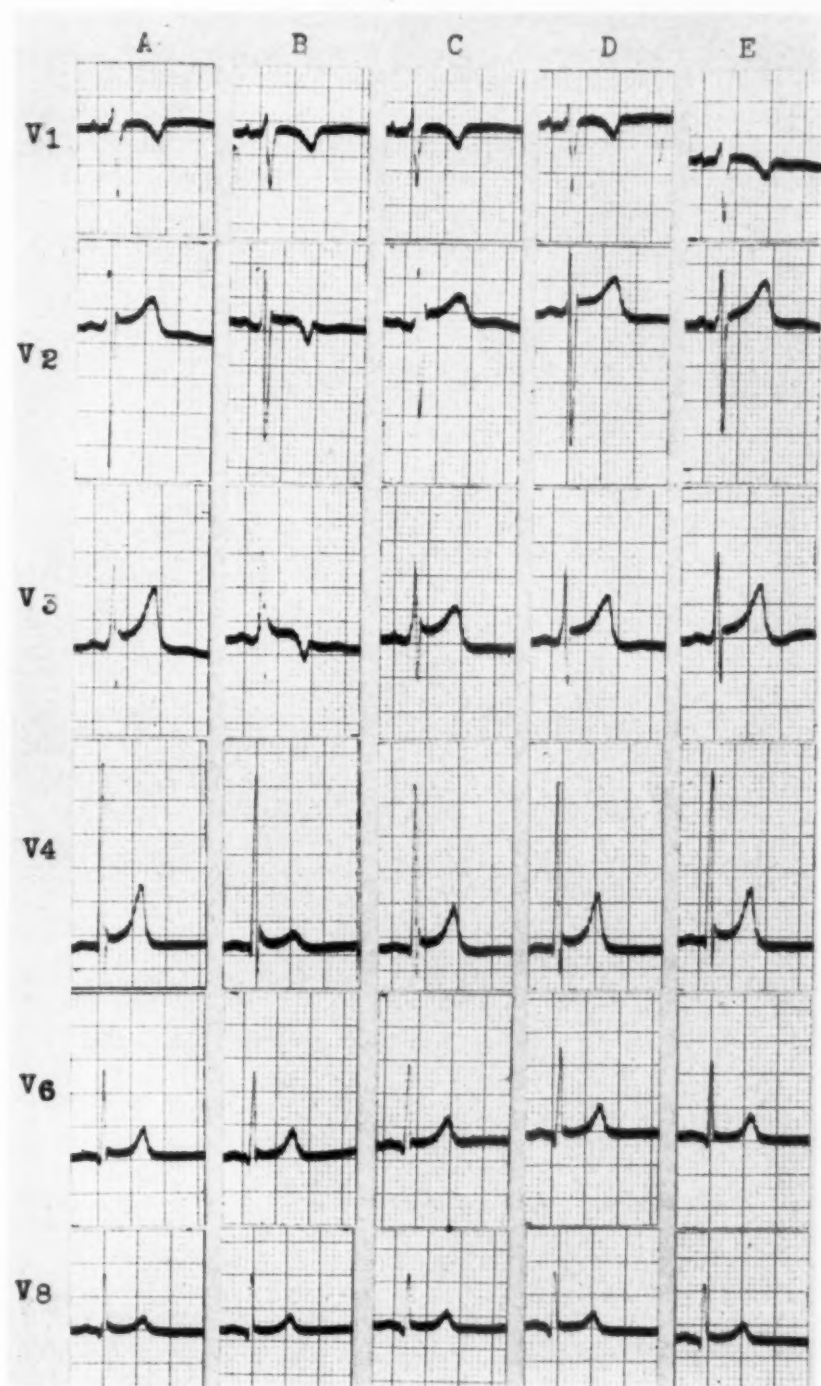Fig. 1.—Electrocardiographic records of subject No. 1. *A*, Control records obtained before cooling the chest wall; *B, C, D*, and *E*, Records obtained 1, 10, 20, and 25 minutes after the ice bag, containing ice-salt mixture, was removed from the chest wall. The records show marked depression of the T wave in Leads V_1 to V_4 as the result of cooling, complete recovery taking place in 25 minutes.

It was noticed that subject 1 with the lowest pelidisi reacted most to the effect of cooling. The precordial lead electrocardiograms of this subject are shown in Fig. 1. They show a pronounced alteration of the T wave. In Fig. 1, B which was taken one minute after cooling, the T wave in Lead V_1 has become more negative and in Leads V_2 to V_4 the T wave is markedly depressed, being negative in Leads V_2 to V_3. In Fig. 2, B the T wave in Leads V_2 and V_3 is also considerably depressed but not so much as to become negative. However, it
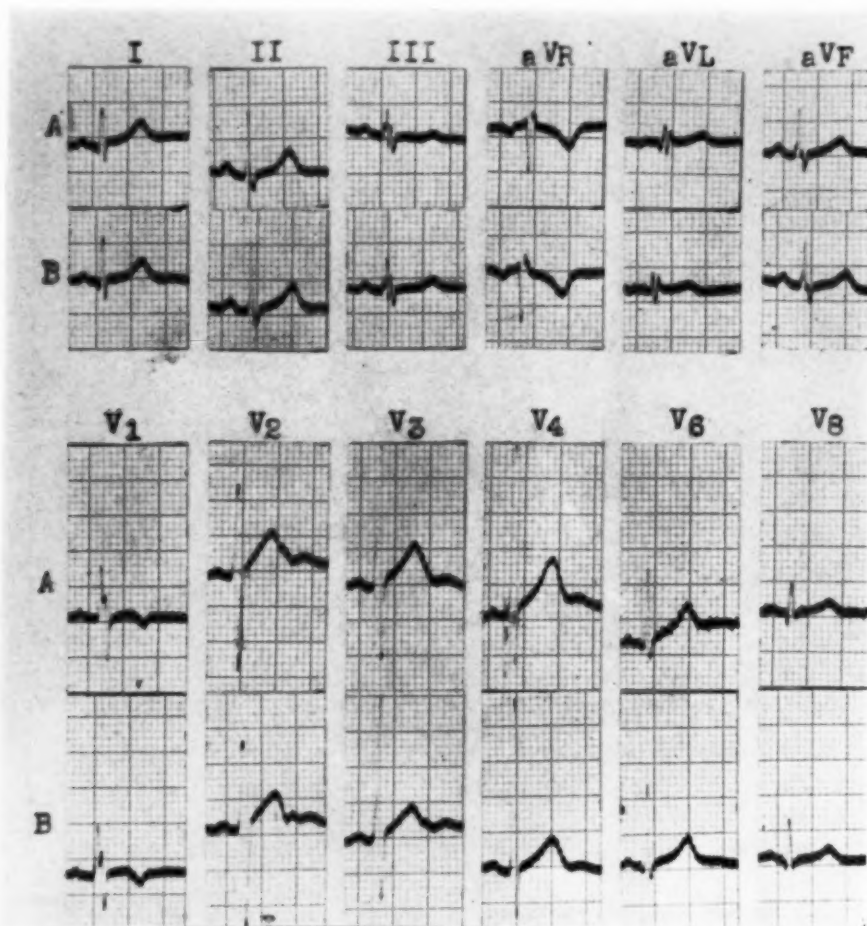
Fig. 2.—Electrocardiographic records of subject No. 14. A, Control; B, Taken immediately after cooling the chest wall. The T wave in Leads III, aV$_F$ and V$_5$ has developed increased positivity. The T wave in Leads V_1 to V_4 is depressed.

shows a small wave or notch in its terminal portion. It has been stated[8] that a marked lowering (50 per cent) of the gradient potential gives rise to notching of the T wave. The notching of the T wave is apparently the result of a considerable depression in its magnitude when, at the same time, the QRS deflections are not materially affected. It is noticed that the U wave is also depressed after cooling.

Cooling the precordial region of the chest wall gave rise to increase in blood pressure in certain subjects as shown in Table I.   In six of the subjects there was no increase in blood pressure.   In three of the subjects the increase was only in the diastolic pressure.   In the rest of the subjects there was an increase in both the systolic and the diastolic pressures.   The largest increase was in subjects 6 and 7, where the systolic pressure went up by 30 mm. and 18 mm., respectively. These subjects may be considered as hyperreactive.   In the rest of the subjects there was an increase in pressure of 5 mm. or slightly more.

This suggests that the chest region is not so sensitive as the hand region for bringing about the pressor response.   In a series of 350 subjects on whom the cold pressor test was performed, Feldt and Wenstrand[9] noticed that the average rise in systolic blood pressure was over 16 mm. with a similar rise in the diastolic pressure.   In hyperreactors the average rise in systolic pressure was found by them to be over 27 mm.   In these tests the hand was dipped in cold water at the temperature of 3° to 5°C. for only one minute.   Whereas in our subjects, though the ice bag was placed on the chest for three minutes before the blood pressure was recorded, the rise in pressure was not so marked.

There was only a very slight change in the heart rate as the result of cooling the precordial region.   We are inclined to believe that the net effect of cooling is to reduce the heart rate slightly and that, in subjects who showed an increased rate, the increase was due to an emotional factor.   In subjects 6 and 7, who showed marked increase in blood pressure, the heart rate was not materially altered; it was slightly slowed in one subject and slightly increased in the other. (Table I).

DISCUSSION

Cooling the precordial surface of the chest wall brings about depression in the amplitude of the T wave in the precordial Leads V_1 to V_4.   The conclusion is drawn that this depression is due to primary T-wave changes resulting from cooling of that portion of the anterior epicardial surface of the heart which is in close proximity to the anterior chest wall.   The reasons for this conclusion follow.

1.   The work of Dowling and Hellerstein[3] shows that drinking 800 c.c. of iced water brings on, in normal subjects, significant T-wave changes in the limb leads and in the unipolar chest leads.   The T wave in Leads I, aV_R, aV_L, and in the right-sided precordial leads tends to become more positive (or less negative), while in the left posterolateral chest leads, and in Leads II, III, and aV_F it tends to become depressed (less positive or more negative).   Presumably, the drinking of iced water gives rise to primary T-wave changes caused by cooling of the diaphragmatic surface of the heart.   If this is correct, then cooling of the anterior surface of the heart should give rise to T-wave changes of the opposite pattern. This is found to be the case.

Cooling of the precordial region of the chest wall gave rise to depression of the T wave in Leads V_1 to V_4.   But there were individual variations.   The depression of the T wave in Lead V_2 was present in all cases.   The depression in Lead V_1 and in Lead V_3 was present in the records of all but three of the subjects.

The depression of the T wave in Lead V_4 was present in the records of all but six of the subjects. In two (Nos. 6 and 8) of these six subjects, the T-wave records in Lead V_4 actually showed increased positivity. As the depression of the T wave was most constantly seen in Lead V_2, one may be justified in concluding that, generally, the heart is nearest the chest surface in this region.

In Lead V_6, the T-wave alteration was not marked. In some of the cases, no alteration in T-wave amplitude was obtained in this lead. In as many cases, there was a slight increase in positivity. In three of the cases, there was a slight decrease in positivity of the T wave. On an average, the T-wave amplitude in Lead V_6 may be said not to alter. In Lead V_8, on the other hand, the records showed increased positivity of the T wave in most of the cases. There was no alteration in a few of the cases.
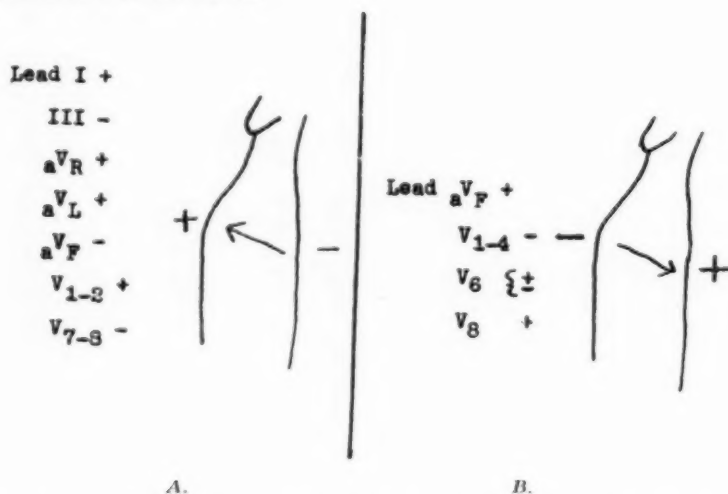

Fig. 3.—(+) indicates absolutely more positive or relatively less negative T waves; (−) indicates absolutely more negative or relatively less positive T waves. The T vector is represented as an arrow which becomes directed away from the region of delayed repolarization. A, Effect of drinking iced water on the T wave (after Dowling and Hellerstein[3]). B, Effect of cooling the precordial region on the T wave. This is mainly opposite to that produced by drinking iced water.

Thus we see that, in the precordial records, there was generally a depression of the T wave in Leads V_1 to V_3 and, to some extent in Lead V_4, and an increased positivity of the T wave in the posterolateral Lead V_8 with an intervening zone between, where there was no change in amplitude of the T wave. Fig. 3, B gives a comprehensive picture of the main T-wave changes which take place as a result of cooling the precordial region of the chest wall. These are opposite in direction to those produced by drinking iced water (Fig. 3, A.).

2. Since the subject lay supine during the experiment, it may be presumed that the position of the heart was not disturbed when the electrocardiographic records were obtained after cooling the chest surface as compared with the position before cooling. One would expect that the anatomical axis would not be altered with the cooling of the anterior chest wall. In such a case, if the T-wave change is primary, one would not expect any material change in the magnitude and the axis of $\hat{A}_{QRS}$ after cooling. This appears to be the case. Table II shows

that the magnitude of $\hat{A}_{QRS}$ as a whole is not materially altered. Though in the records of individuals there is a marked fluctuation in the magnitude of $\hat{A}_{QRS}$, this is likely to be caused by the margin of error and personal factor involved in the method used for the estimation of the magnitude. But these errors are likely to neutralize themselves in the aggregate result from the sixteen subjects, and the over-all picture is likely to give a fairly accurate idea of the average change in magnitude.

The axis of $\hat{A}_{QRS}$ shows a very slight shift to the right (about 1.4°), possibly caused by a slight anticlockwise rotation of the heart on its long axis as a result of cooling of the chest wall. The axis of $\hat{G}$ on the other hand has rotated slightly (about 2°) towards the left (clockwise). This rotation of the axis of $\hat{A}_{QRS}$ and of $\hat{G}$ in opposite direction may be ascribed to the effect of cooling. The rotation of the axis of $\hat{G}$ towards the left is also significant. Generally, if local ischemia involves that portion of the ventricular muscle which is irrigated by the right coronary artery, the manifest gradient $\hat{G}$ sweeps through a positive rotation. On the other hand, if the local ischemia involves that portion of the ventricular muscle which is ordinarily irrigated by the left coronary artery, the manifest gradient $\hat{G}$ sweeps through a negative rotation.[10,11]

Table II gives the effect of cooling on the magnitude and deviation of the manifest ventricular gradient $\hat{G}$.

The effect on the electrocardiogram of drinking iced water has been found[3] to be a tendency for $\hat{G}$ to move to the right (counterclockwise) towards the first and second sextants. In the present group of cases there is a tendency, though slight, for $\hat{G}$ to move towards the left. This again is in keeping with the general finding that the T-wave changes brought about by cooling the precordial region of the chest are, in the main, opposite in pattern to those brought on by drinking iced water. Table II shows that in a few of the subjects the ventricular gradient did not show rotation to the left after cooling. The position of the heart may, to a certain extent, be a determining factor. In whichever direction the gradient may shift, the T-wave changes are evidently primary as they are not accompanied by any significant change in the shape or size of QRS.

3.   It may be argued that the T-wave changes caused by application of cold to the chest may be due to nervous reflexes originating from the cooled area and reflexly bringing about coronary vasoconstriction and myocardial ischemia in the same way as they bring about peripheral vasoconstriction and rise of blood pressure. But, apparently, this is not likely. In subject 1, whose electrocardiogram is shown in Fig. 1, the ice bag was placed on the anterior abdominal wall for seven minutes. This gave rise to no change in the electrocardiographic features. Neither did similar cooling of the right anterior chest wall give rise to any electrocardiographic change, although it gave rise to an increase in blood pressure. Evidently, the T-wave changes appear only when that part of the chest wall which lies close to the heart is cooled.

More marked T-wave changes are seen in the case of thin subjects with a thin chest wall. Subjects with lower pelidisi generally show more marked T-wave changes than subjects with higher pelidisi. Table III indicates the alteration in the amplitude of T wave in Lead V_2, after cooling, in the records of subjects

TABLE II

SUBJECT NO.	MAGNITUDE (UNITS)				AXIS				ANGLE BETWEEN Âqrs AND Ĝ	
	Âqrs		Ĝ		Âqrs		Ĝ			
	BEFORE COOLING	AFTER COOLING	BEFORE COOLING	AFTER COOLING	BEFORE COOLING	AFTER COOLING	BEFORE COOLING	AFTER COOLING	BEFORE COOLING	AFTER COOLING
1	6.6	5.8	12.5	12.8	53	50	52	55	1	−5
2	2.1	3.2	8.3	7.9	80	81	53	53	27	28
3	5.4	5.7	17.3	10.4	85	85	84	84	1	1
4	3.5	3.5	6.1	6.5	44	42	25	40	19	2
5	3.5	2.6	10.0	8.0	24	30	−4	10	28	20
6	5.6	4.9	11.4	11.0	80	76	76	73	4	3
7	5.3	5.5	10.5	12.4	83	77	64	65	19	12
8	5.4	5.6	17.6	17.1	76	80	68	73	8	7
9	4.3	4.7	7.6	9.5	20	17	19	18	1	−1
10	7.5	6.5	13.2	12.5	65	69	55	55	10	14
11	5.5	5.0	21.5	11.1	87	84	86	86	1	−2
12	8.8	7.0	15.3	12.4	74	72	50	49	24	23
13	9.1	8.4	19.2	19.4	78	74	62	57	16	17
14	2.5	2.5	10.0	9.2	52	46	42	44	10	2
15	3.0	4.0	6.8	10.1	52	45	38	37	14	8
16	4.8	5.0	17.3	18.3	72	74	74	77	−2	−3
Average	5.17	4.99	12.79	11.79	64.06	62.62	52.75	54.75	11.31	7.87

whose pelidisi was below 90 as compared with the alteration in the same lead in the records of subjects with pelidisi of over 90.   In the former group the depression in amplitude of T wave, after cooling, was over 31 per cent, whereas in the latter group the depression in amplitude was about 15 per cent.   The inference is that cold can penetrate more easily to the heart through a thin-walled chest than through a thick-walled chest.   If the T-wave changes were due to nervous reflexes one would have expected equal reaction in both groups of subjects.

TABLE III

SUBJECT NO.	SUBJECTS WITH PELIDISI BELOW 90		SUBJECT NO.	SUBJECTS WITH PELIDISI ABOVE 90	
	HEIGHT OF T WAVE IN LEAD V_2 (MM.)			HEIGHT OF T WAVE IN LEAD V_2 (MM.)	
	BEFORE COOLING	AFTER COOLING		BEFORE COOLING	AFTER COOLING
1	4.0	−1.5	2	7.5	7.0
3	6.1	4.8	5	10.7	7.5
4	8.7	6.2	6	5.8	5.4
11	4.2	3.2	7	9.0	7.0
14	6.0	4.5	8	18.2	16.0
16	12.2	11.0	9	4.0	3.7
			10	10.7	10.6
			12	11.2	9.5
			13	8.5	5.0
			15	11.0	10.0
	41.2	28.2		96.6	81.7
6	Percentage alteration after cooling = 31.5		10	Percentage alteration after cooling = 15.4	

The same argument applies against the possibility of a chemical factor arising from the cooled area of the chest wall, because in such a case the chemical substance would have affected the heart as a whole and not specific regions of the heart in a differential manner.   Besides, such a chemical substance would have been produced by cooling any part of the chest wall and not the precordial region alone.

Another consideration is the duration through which the T-wave changes last.   The T-wave changes caused by drinking iced water last for about 25 minutes.[3]   Those caused by cooling the chest wall also last for about the same time after the cooling is discontinued, as was seen in the case of subject 1 (Fig. 1). However, we did not investigate this in other subjects but are inclined to believe that there might be slight variation in time depending on the degree of cooling of the chest wall.   As the duration of the T-wave changes is more or less the same in both cases, these changes are evidently caused by the same factor.

SUMMARY

Electrocardiographic records were obtained in sixteen subjects, with apparently normal hearts, before and after cooling the precordial region of the chest wall by placing an ice bag on it for five to six minutes. Cooling the chest wall gave rise to depression of the T wave in Leads V_1 to V_4. This was associated, in most cases, with increase in positivity of the T wave in Leads aV_F and V_8. The T-wave changes resulting from cooling the chest wall were, in the main, of opposite pattern to those resulting from drinking iced water.

More marked T-wave changes were obtained from subjects with a thinner chest wall and lower pelidisi as compared with subjects with a thicker chest wall and higher pelidisi. The T-wave changes lasted for about twenty-five minutes. The ventricular gradient shifted, on the average, slightly (about 2°) to the left.

The T-wave changes were not related to the increase in blood pressure which occurred in most, but not all, of the subjects as a result of cooling the chest wall. The Q-T interval was not markedly altered. Cooling the chest wall on the right side, away from the heart region, or cooling the abdominal wall, did not give rise to electrocardiographic changes, although it gave rise to an increase in blood pressure.

CONCLUSION

Cooling the precordial area of the chest wall gives rise to primary T-wave changes. It is suggested that these changes are due to delayed repolarization of the epicardial surface of the anterior heart wall resulting from the actual cooling of the surface of the heart in this region.

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THE ROLE OF AUSCULTATION IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE

A Phonocardiographic Study of Children

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INTRODUCTION

ACCURATE diagnosis of congenital heart disease is of great practical importance today. Radiologic, electrocardiographic, angiocardiographic, and cardiac catheterization studies on the subject have been published in abundance. The role of auscultation, however, has generally been understated. The present phonocardiographic study of congenital cardiac conditions is published primarily to demonstrate the auscultatory phenomena detectable by the careful use of the stethoscope. It is only a secondary purpose of this paper to advocate the use of phonocardiography in the differential diagnosis of congenital heart disease.

MATERIAL

Sixty-four patients, between the ages of 5 and 15 years, suffering from congenital heart disease were included in this study. These comprised cases of aortic stenosis, isolated pulmonary stenosis, atrial septal defect, ventricular septal defect, tetralogy of Fallot, and atypical cases of patent ductus arteriosus.

In all cases, save those of aortic stenosis, the diagnosis was confirmed by cardiac catheterization, by operation, or in a few by autopsy. In the cases of aortic stenosis, the diagnosis was arrived at by clinical, electrocardiographic, and radiologic means and by analysis of carotid artery tracings.

The division of the pulmonary stenosis patients—"isolated" or with overriding aorta—into valvular and infundibular types was possible with assurance only on the basis of findings at operation or in a few instances by means of clearcut catheter findings. In others, division into these two categories was made only tentatively on the basis of presence or absence of poststenotic dilatation of the pulmonary artery or by less well-defined catheter findings.

METHODS

All recordings were made with the Sanborn Twinbeam Stetho-Cardiette using stethoscopic and logarithmic microphones. Recordings were taken routinely from the apex, the fourth, and second left intercostal spaces, and the second right intercostal space parasternally. This apparatus and technique have been described by Rappaport and Sprague.[1,2]
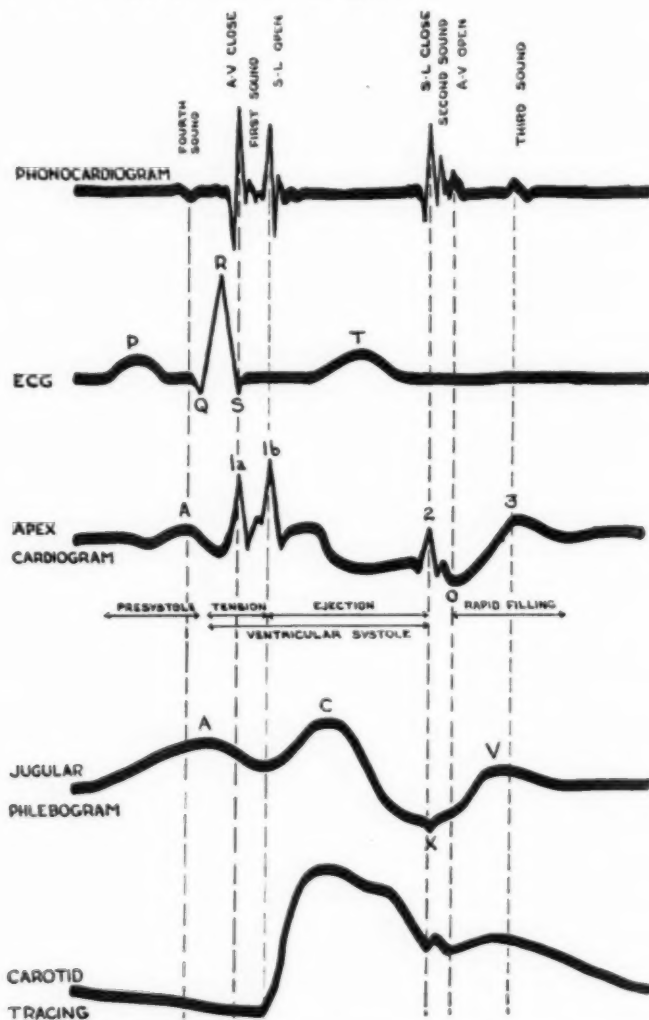

Fig. 1.—The normal heart sounds and their identification by reference tracings (After Luisada[15]).

For reference tracings, the electrocardiogram (Lead II) and the apexcardiogram[15] have been used throughout. Jugular phlebograms and carotid pulse tracings were obtained whenever it was technically possible.

*Normal Heart Sounds and Their Identification by Reference Tracings (Fig. 1).** —Four heart sounds are normally registered on the stethoscopic tracing taken at

*This diagram is a modification of the one used by Luisada in the chapter on phonocardiography in his book.[15]

the apex. The third heart sound, best identified by the 3 wave of the apexcardiogram, corresponds to the onset of the first rapid filling period in diastole.[3] The fourth or auricular sound, corresponding to the second rapid filling period, follows the P wave on the electrocardiogram and coincides with the "a" wave of the apexcardiogram and the jugular phlebogram. In this study we have not found the patterns of the third and fourth heart sounds to be of great significance; hence, they will not be discussed in detail.

In contrast, the first and second sound complexes have been of great significance and will be discussed in considerable detail.

The first sound complex, which immediately follows the Q wave on the electrocardiogram and ends with the C wave of the jugular venous pulse, is comprised of four components.[4,5] Of these, the first and fourth—the auricular and vascular components—are of low amplitude and frequency and may be difficult to identify. The second and third components, consisting of valvular elements, are readily distinguishable and have been of considerable interest in the study of our patients.

The second component of the first sound complex represents auriculoventricular valve closure and is simultaneous with the 1a wave of the apexcardiogram and closely follows the apex of the QRS complex of the electrocardiogram. The third component, usually separated from the second by an appreciable interval, represents semilunar valve opening and coincides with the 1b wave of the apexcardiogram, the rise of the C wave on the phlebogram, and the upstroke of the carotid pulse.

The second sound complex, beginning with or shortly before the 2 wave of the apexcardiogram and ending with the O point of the apexcardiogram or the V wave of the jugular pulse, is also composed of four components.[2] The first and third of these, originating in the heart muscle and the vessel walls, are usually difficult to demonstrate and are of no practical importance for the purposes of this study.

The second component consists of high amplitude vibrations of many frequencies and is due to semilunar valve closure. It may be identified by the 2 wave on the apexcardiogram, the point of maximum systolic collapse (x) on the phlebogram, and the dicrotic notch on the carotid tracing. The fourth component of the second sound complex is due to auriculoventricular valve opening and is normally not registered with the logarithmic microphone. In the stethoscopic tracing, it consists of one or two low-frequency, low-amplitude vibrations, and corresponds to the O wave on the apexcardiogram and precedes the V wave of the jugular venous pulse.

One aspect of the second sound complex in which we have been particularly interested was the identification of the elements of the second or semilunar component. It has been shown that this component is made up of aortic and pulmonary elements occurring either synchronously or asynchronously.[6] When the valves close synchronously, a narrow semilunar component without appreciable splitting will result. If, however, the valves close asynchronously, as is thought to be the case in the majority of normal children,[7] identification of the aortic and pulmonary elements may be attempted. It has been shown[8] that aortic valve closure coincides with the dicrotic notch on the carotid tracing.

Hence, if splitting of the semilunar component is recorded, with the first element corresponding to the dicrotic notch, it can be justifiably presumed that the second element corresponds to pulmonary valve closure. That this element is not due to auriculoventricular valve opening is suggested by the characteristics of its vibrations and proved by the fact that it precedes the O point of the apex-cardiogram.
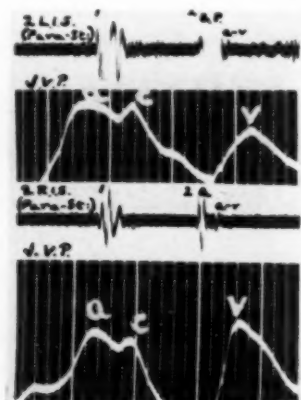

Fig. 2.—The identification of the valvular components of the second heart sound in the phono-cardiogram of a normal child. Note the separation of the aortic and pulmonary components of the second heart sound at the second left intercostal space and the presence of only one component—the aortic—at the second right intercostal space.

JVP = jugular venous phlebogram; 2Lis = second left intercostal space; 2 Ris = second right inter-costal space; A = aortic; AV = auriculoventricular; P = pulmonary; Parast = parasternal.

Another method by which the elements of the semilunar component of the second sound may be identified is represented in the tracings from a normal child (Fig. 2). Here, the first high amplitude element is well registered both at the second left and second right intercostal spaces, whereas the second high amplitude vibration is registered only at the second left intercostal space. By inference, then, it may be assumed, that the high-frequency, high-amplitude element of the semilunar component, best registered at the second left intercostal space probably corresponds to pulmonary valve closure, whereas the earlier vibrations of the same character, demonstrated both at the second right and left intercostal spaces, probably originate at the aortic valve.

RESULTS

A. *Aortic Stenosis.*—Eleven cases were studied and a composite diagrammatic chart of the findings is shown in Fig. 3. A representative tracing is presented in Fig. 4.

The first sound complex in this condition is characterized by high-amplitude, medium-frequency vibrations, corresponding with semilunar opening, best registered at the second right intercostal space and always less than 0.03 sec. in duration.

The auriculoventricular component of the first sound was poorly registered in all areas in seven of the eleven cases, and normally registered at the apex in the remaining four cases.

The semilunar component of the second sound complex was narrow in all instances, never exceeding 0.04 sec. in the stethoscopic tracing at the second right intercostal space.   In only three of the eleven cases (4, 9, and 11) was appreciable splitting demonstrated.
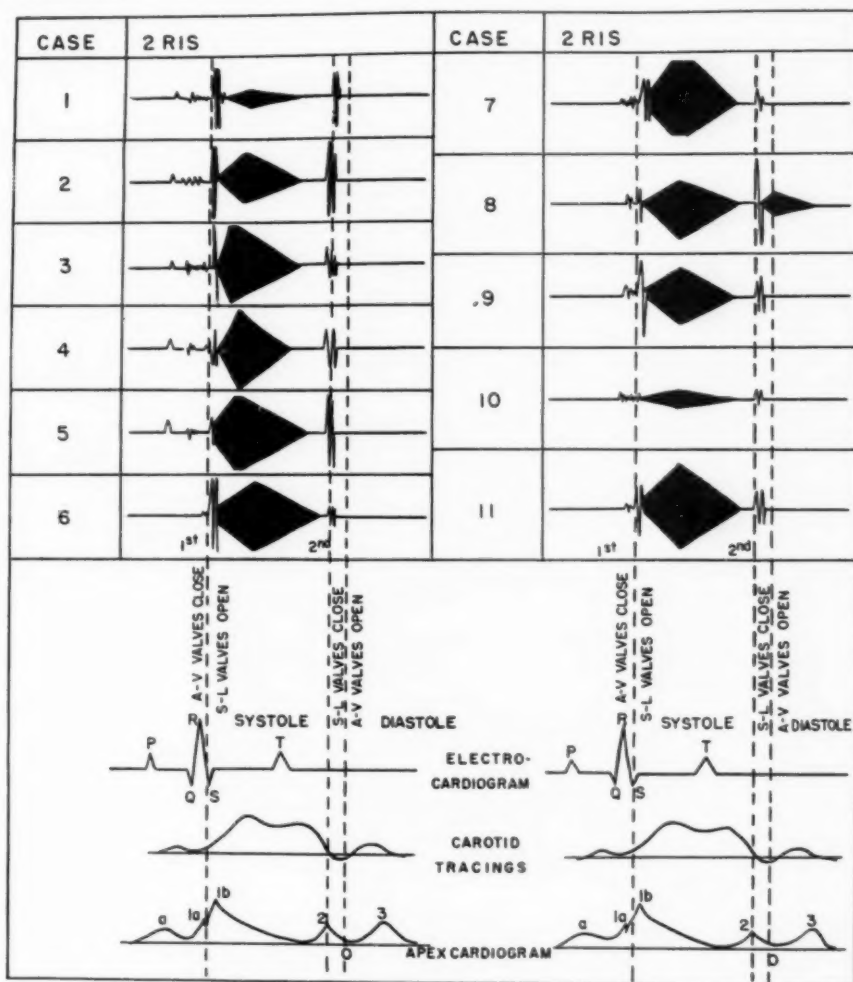

Fig. 3.—Diagrammatic representation of the phonocardiogram in congenital aortic stenosis.

The systolic murmur consists of high-amplitude, high-frequency vibrations. It is always best registered at the second right intercostal space and is of diamond configuration with the apex of the diamond at the end of the first third of systole. The murmur always begins with the first sound and ends an appreciable interval before the second sound.   A typical murmur of aortic incompetence[9] was recorded in only one case (Case 8).   This started immediately after the second sound with a rapid crescendo, followed by a longer decrescendo, fading out halfway through diastole.

The systolic murmur transmits invariably very well to the neck and the shoulders and the back.

B.   *"Isolated" Pulmonary Valvular Stenosis.*—Ten cases were studied and the results are diagrammatically represented in Fig. 5.   Six cases (1, 3, 5, 6, 8, and 9) with a pressure gradient from right ventricle to pulmonary artery of more than 75 mm. Hg were classed as severe.   The remaining four patients (2, 4, 7, and 10) with gradients of a lesser magnitude were classed as mild.
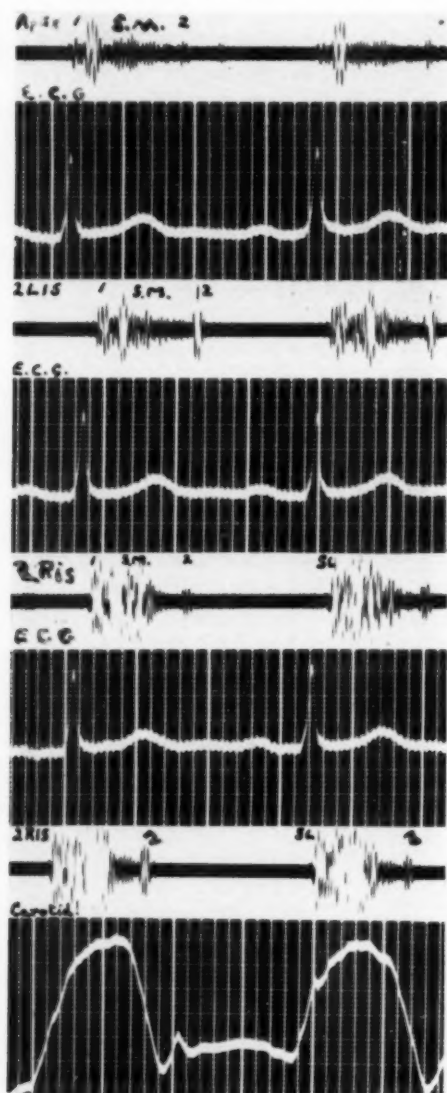

Fig. 4.—Phonocardiogram from a case of congenital aortic stenosis.   1 = first sound;   2 = second sound;   SL = semilunar;   SM = systolic murmur.

The auriculoventricular component of the first sound complex was well registered in all cases but one.   In the majority of instances (six out of eleven), the amplitude of these vibrations was higher than usual at the second left inter-costal space.   The semilunar component, by contrast, was absent or diminished in all but the four mildest cases.   The accentuation of this component in in-stances of mild pulmonic stenosis has been noted clinically.[16]

In the severe cases of stenosis, the semilunar component of the second sound was single, or narrowly split, with the late and presumably pulmonary valve element being of low amplitude (Fig. 6A, stethoscopic tracing).   In the milder degrees of stenosis (2, 7, and 10), the semilunar component was fairly well split with the pulmonary valve element being of normal or only slightly diminished amplitude.   An "opening snap" was present in Case 8, without any other clinical or catheterization evidence of mitral stenosis.
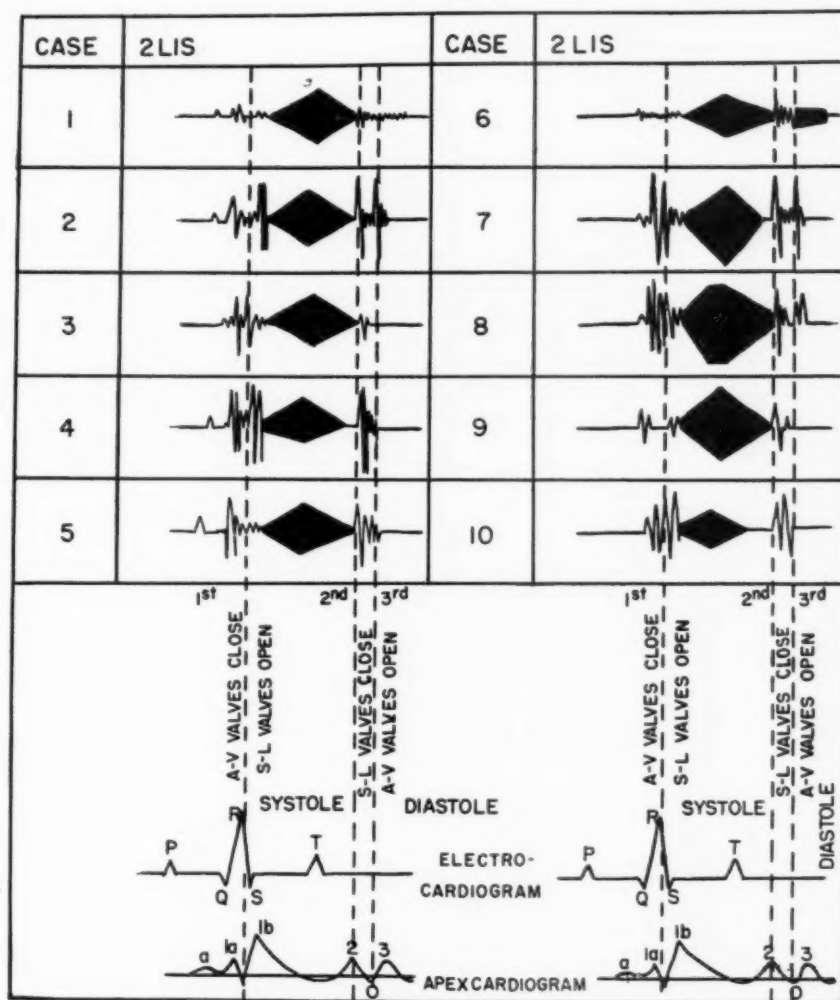

Fig. 5.—Diagrammatic representation of the phonocardiogram in isolated valvular pulmonic stenosis.

The characteristic systolic murmur of this group of patients was diamond shaped with the apex of the diamond in mid-systole (Fig. 6B, logarithmic tracing). The vibrations were of high frequency and high amplitude, starting immediately after the first sound and occupying, in all but the three mildest cases, the whole of systole.   In every case, the murmur was best registered at the second left intercostal space.   This murmur transmits extremely well to the neck, shoulders, and back, much like the systolic murmur of aortic stenosis.   A differential point

between the two conditions may be found in that the aortic stenosis murmur
transmits better to the right side of the neck and the pulmonic one rather to the
left. (This is a rule not without exception, however.) In four patients with
maximal pulmonic stenosis (1, 5, 6 and 9), a gap between the first sound and the
onset of the murmur is suggested in some tracings. Reference to the apexcardio-
gram and the phlebogram demonstrates, however, that this is due to the dim-
inished semilunar component of the first sound and that the murmur does, in
fact, start with the onset of systole. Extension of the systolic murmur into early
diastole occurs only in the most severe cases (1, 6). Another three cases with
severe pulmonic stenosis showed low-frequency, low-amplitude mid-diastolic
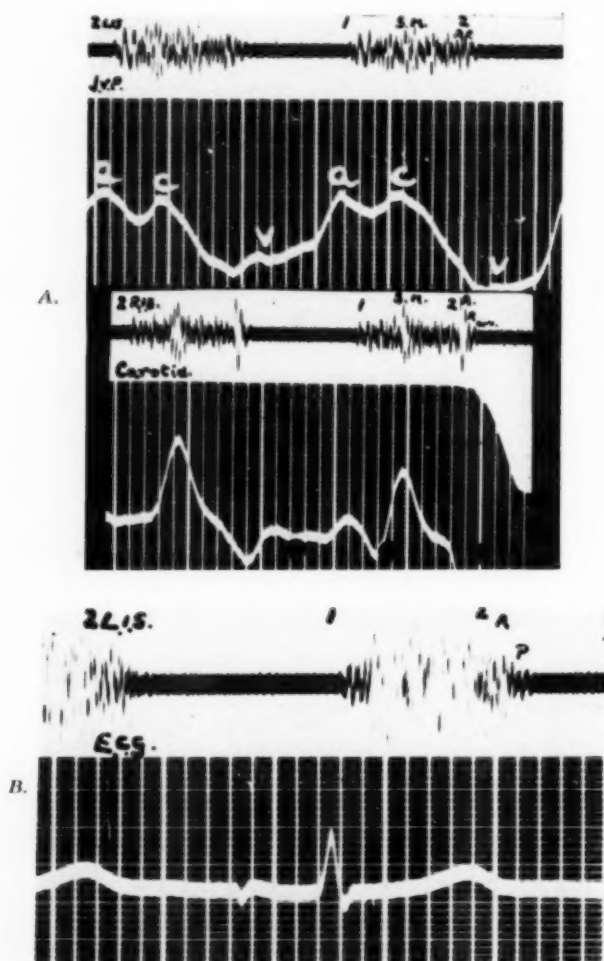murmurs at the apex or the fourth left intercostal space.

Fig. 6.— A, Stethoscopic phonocardiogram in a patient with valvular pulmonic stenosis. Note
the low-amplitude semilunar components of the second sound at the second left intercostal space and
the single aortic component at the second right intercostal space.   B, Logarithmic phonocardiogram
at the second left intercostal space of patient with valvular pulmonic stenosis.
    JVP = jugular venous phlebogram; 1 = first sound; 2 = second sound; SM = systolic murmur;
A = aortic; P = pulmonary; AV = auriculoventricular.

C.   *Ventricular Septal Defect and Single Ventricle.*—Eighteen cases of ventricular septal defect or functionally single ventricle were studied and a composite diagram of the phonocardiographic appearances is shown in Fig. 7.   In the majority of these cases, there was a shunt of blood between the ventricles of 2.5 L./min./M.^{2} or over, ranging up to a maximum of 23 L./min./M.^{2} (The right ventricular systolic pressures were within systemic range in all these cases.)
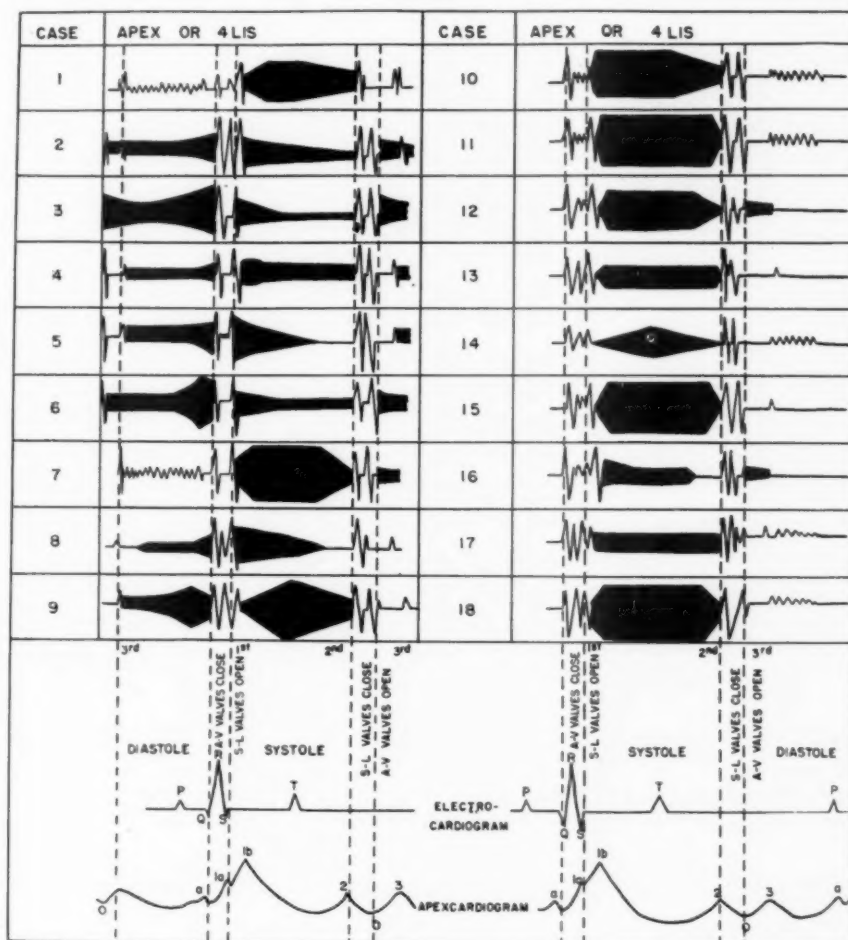

Fig. 7.—Diagrammatic representation of the phonocardiogram in ventricular septal defect and single ventricle.

The first sound complex was not remarkable in any instance.

There was moderate splitting (0.04 to 0.07 sec.) of the semilunar component of the second sound.   The pulmonary elements consisted of unusually high-amplitude vibrations at the second left intercostal space.

The systolic murmur was plateau shaped in ten cases (Fig. 8), decrescendo in six instances (Fig. 9), and diamond shaped in two patients.   The vibrations were usually of high amplitude and high frequency and occupied all of systole.

The murmur was well registered in all instances at the fourth left intercostal space; when a tracing could be obtained from over the xiphoid process, the murmur proved to be at least as loud here as at the fourth left intercostal space. The transmission of this murmur to the neck and back was not nearly as good as that of the systolic murmur of the stenotic lesions.
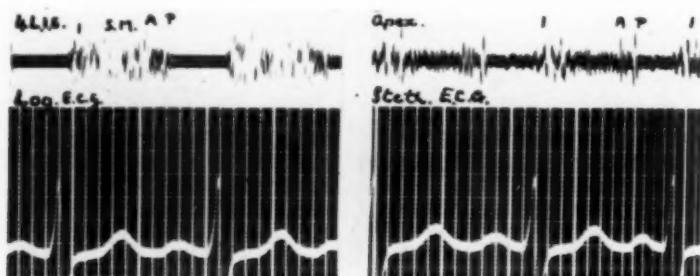

Fig. 8.—Phonocardiogram with reference to electrocardiogram in a patient with ventricular septal defect. Note the high-amplitude pulmonary component of the second sound. See legend of Fig. 6 for abbreviations.

Three types of diastolic murmurs were recorded: (1) low-amplitude, low-frequency, apical mid-diastolic murmurs, sometimes continuing into presystole without crescendo (Fig. 10: logarithmic tracing); (2) high-frequency and often high-amplitude vibrations throughout diastole or following the third sound and continuing into presystole with a crescendic configuration in many instances (Fig. 9); (3) early, high-frequency, low-amplitude diastolic murmurs, of the semilunar insufficiency type.

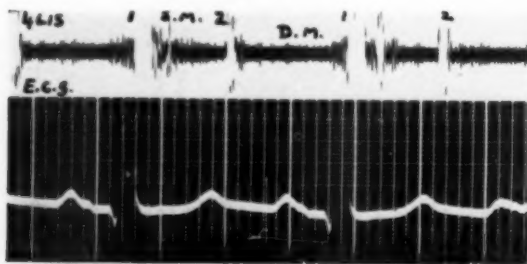Fig. 9.   Fig. 10.

Fig. 9.—Phonocardiogram with reference to electrocardiogram in a patient with large ventricular septal defect showing crescendo presystolic murmur and decrescendo systolic murmur. See legend of Fig. 6 for abbreviations.
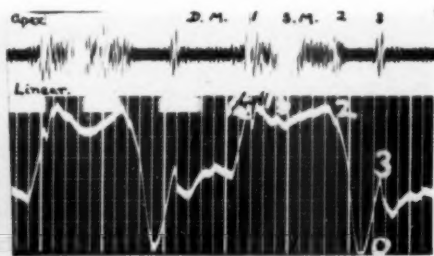
Fig. 10.—Phonocardiogram with reference to linear cardiogram (apexcardiogram) in a patient with a functionally single ventricle. Note presystolic murmur without crescendo.

An attempt was made to correlate these findings with the size of the left-to-right shunt. While, in general, it was difficult to find close correlation, those with a presystolic murmur were all cases in whom either the defect was very large or in which there was a functionally single ventricle. On the other hand, there were several large defects without presystolic murmurs.

D. *Atrial Septal Defect*.—Eleven cases were studied and the phonocardio-graphic findings are shown diagrammatically in Fig. 11. In all these cases, there was incomplete or complete right bundle branch block in the electrocardiogram.[14]

The first sound complex was not remarkable, though usually split more than average.
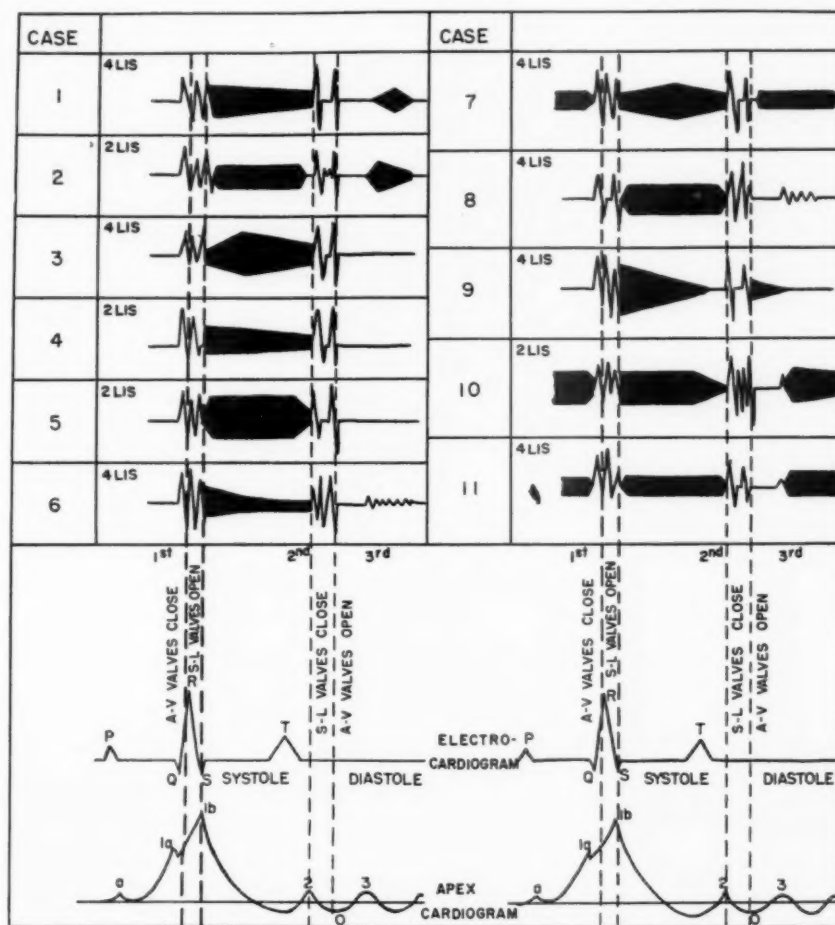
Fig. 11.—Diagrammatic representation of the phonocardiogram in atrial septal defect.

There was marked splitting of the semilunar component of the second sound in every case, (Fig. 12), commonly associated with splitting of the *2* wave of the apexcardiogram. The separation of the aortic and pulmonary valve elements was 0.05 to 0.08 sec. on the stethoscopic tracing. In nine out of eleven cases, the duration between the two elements was 0.07 sec. or more. The pulmonary element, although of quite high amplitude, was generally of considerably lower intensity than in the cases of large ventricular septal defects or single ventricles. (The right ventricular systolic pressures were slightly, if at all, elevated in these patients.)

The systolic murmur, usually plateau-shaped or of decrescendo configuration, was maximal at the second or fourth left intercostal space and transmitted very poorly. The murmurs were all of lower amplitude than that seen with ventricular defects. This may explain the absence of a palpable thrill in these patients.

Diastolic murmurs were observed in eight of our eleven cases (Fig. 11). In two instances, these were low-frequency, low-amplitude vibrations, occupying mid-diastole (Fig. 12). In five other instances, the diastolic murmur consisted of high-frequency, low-amplitude vibrations, starting with the third sound and often extending into presystole. Both these murmurs were best registered at the apex or the fourth left intercostal space. A third type of diastolic murmur, representing high-frequency, low-amplitude vibrations, following immediately the second sound, was registered in one of our patients (Case 9) at the fourth left intercostal space.
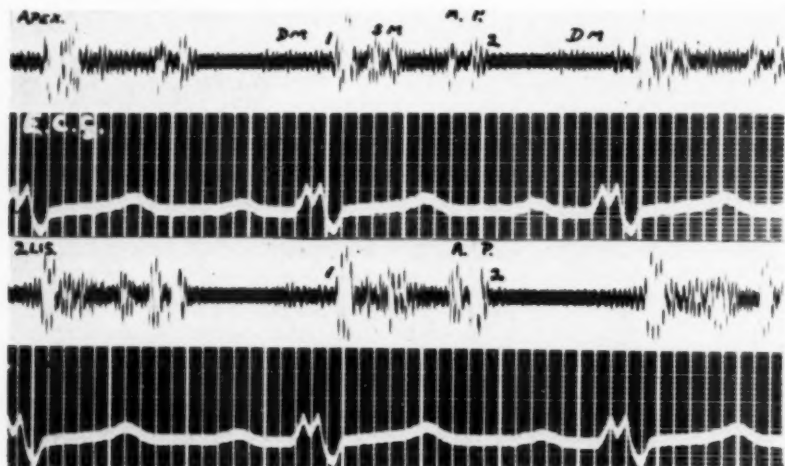

Fig. 12.—Stethoscopic phonocardiogram in a patient with atrial septal defect. Note the mid-diastolic and presystolic murmur without crescendo, also the low-amplitude systolic murmur. The semilunar elements of the second sound are widely separated.

With the jugular phlebogram, used as a reference tracing in eight of our atrial septal defect patients, certain characteristic patterns have been observed (Fig. 13, A and B). Deep systolic collapse followed by a rapid rise to an unusually tall, peaked V wave was observed in all cases. Average or unusually tall A waves were observed in six out of our eight patients. In the remaining two, the A wave was replaced by a marked presystolic collapse (Cases 4 and 6). C waves appeared of average amplitude in all cases.

E. *Tetralogy of Fallot.*—Seven cases were studied and a composite diagrammatic chart is shown in Fig. 14. Of these cases, all save Case 6 had infundibular pulmonic stenosis, as far as could be judged by clinical and catheterization studies or at operation.

The auriculoventricular component of the first sound was of high or medium amplitude at the apex or fourth left intercostal space, whereas the semilunar component was barely recorded.

B.

A.
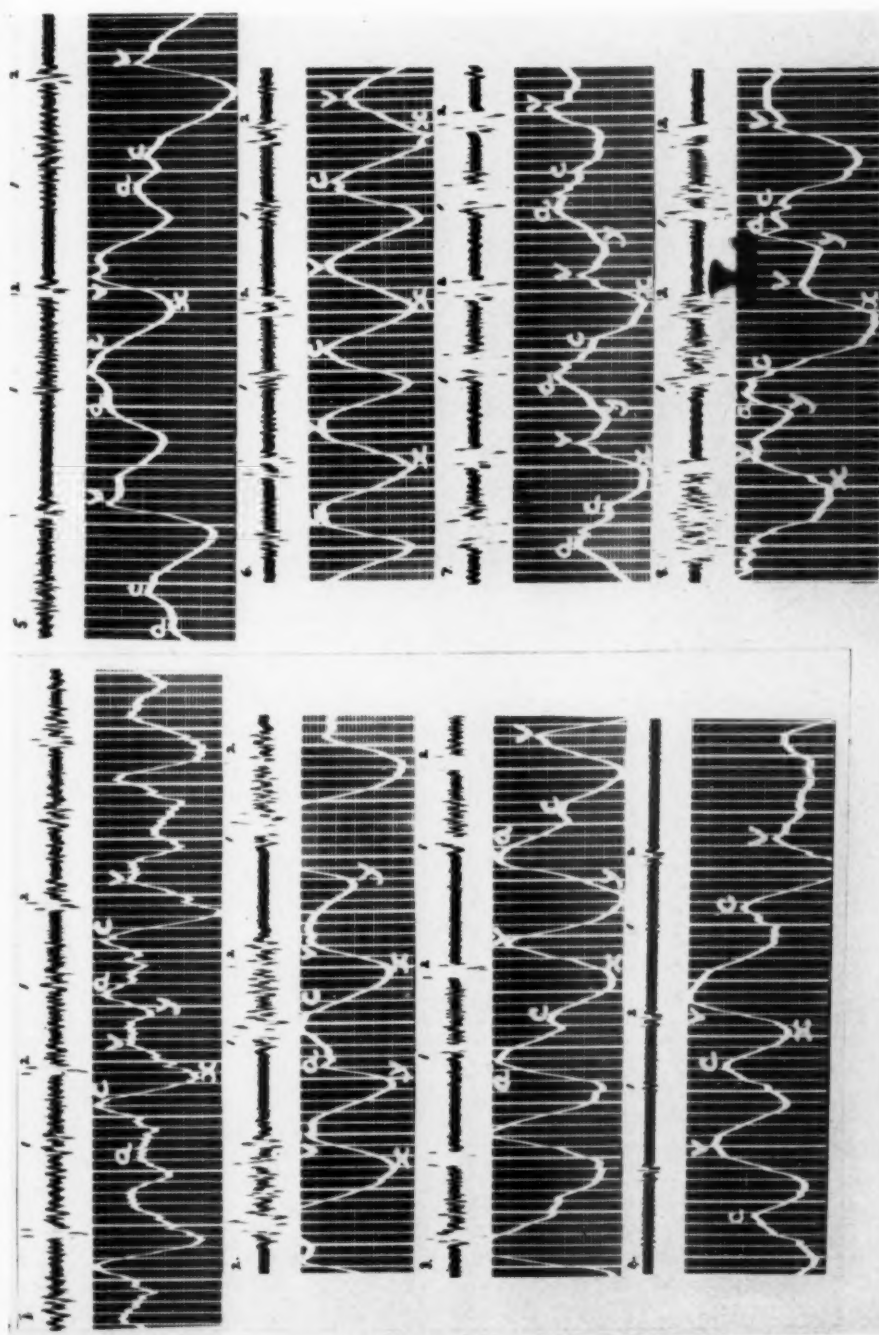
Fig. 13.—A. and B.   Jugular phlebograms in eight cases of atrial septal defect.

The second sound was well registered at the apex and the fourth left inter-
costal space but barely discernible at all at the second left intercostal space.
The semilunar component of the second sound was represented by a single or
narrowly split (less than 0.04 sec.) vibration.   The aortic element of this com-
ponent was of high amplitude in six out of seven cases, and the pulmonary ele-
ment, if present at all, was of low amplitude throughout (Fig. 15).

Fig. 14.   Diagrammatic representation of the phonocardiogram in tetralogy of Fallot.

Fig. 15.—Phonocardiogram in a patient with tetralogy of Fallot.   Note diamond-shaped systolic
murmur and diminished pulmonary valve closure.

The systolic murmur was diamond-shaped and identical in configuration with that demonstrated in the cases with "isolated" pulmonic stenosis. In four cases, the murmur was maximal at the fourth left intercostal space; in three ins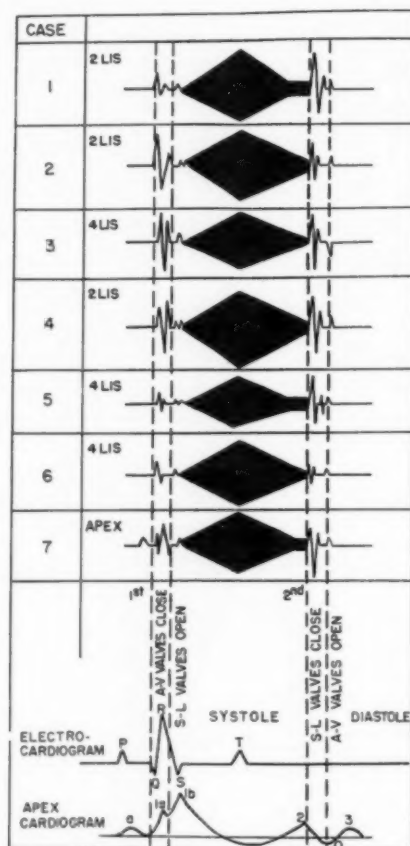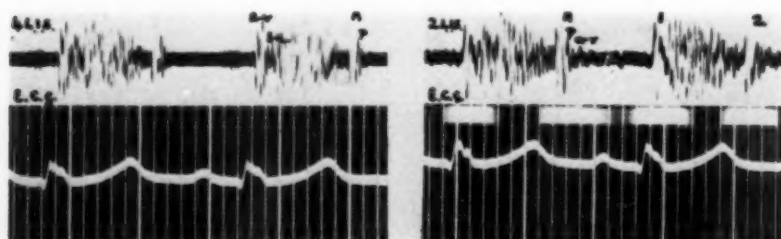tances, it was best registered at the second left intercostal space. A short, low-amplitude, high-frequency presystolic murmur was registered at the fourth left intercostal space in one of our cases.

F. *Atypical Patent Ductus Arteriosus.*—Seven cases were studied and the findings are shown diagrammatically in Fig. 16. The qualification "atypical" refers to those cases in which a continuous systolic-diastolic murmur was not present. The phonocardiographic appearances of the "typical" murmur in this condition have been well described previously[10] and are demonstrated in Fig. 17.

In our "atypical" cases the first sound complex was always normally registered with maximal intensity at the apex.
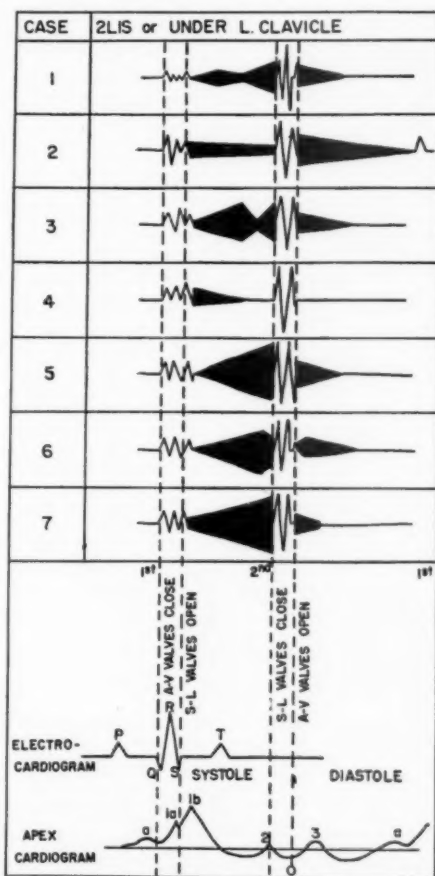

Fig. 16.—Diagrammatic representation of the phonocardiogram in "atypical" cases of patent ductus arteriosus.

The second sound tended to be obscured by the murmur, but the semilunar component was well registered and appeared to be split in all cases. In some instances, the pulmonary element was of higher than normal amplitude.
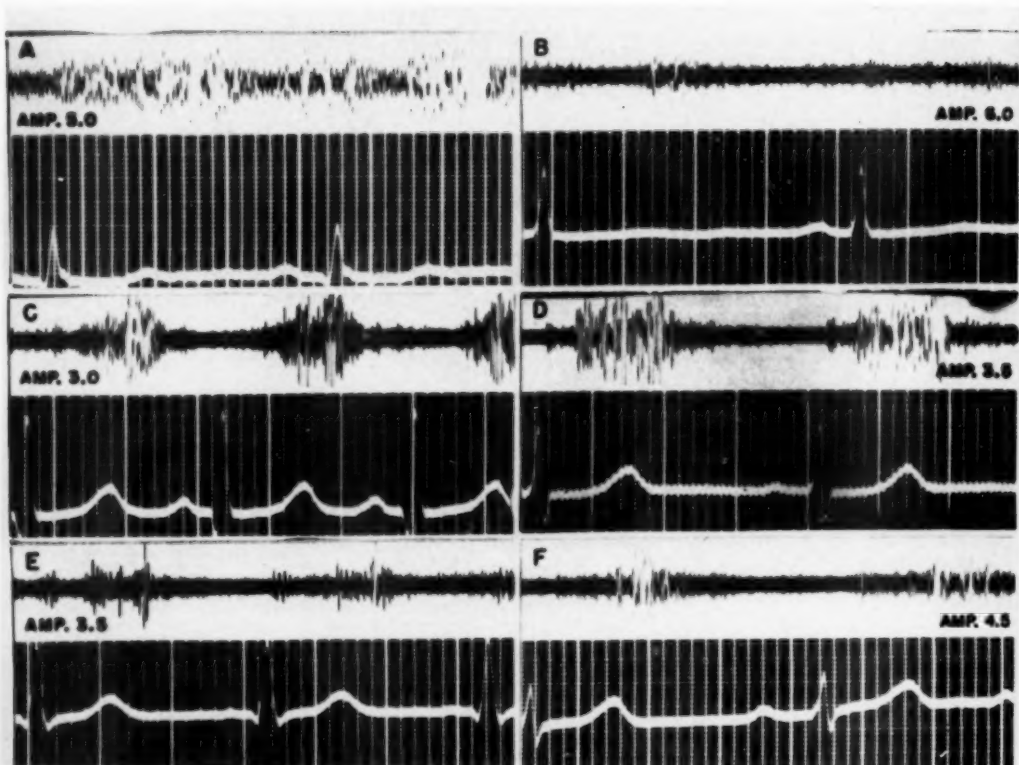
Fig. 17.—Logarithmic phonocardiograms over pulmonic area in six cases of patent ductus arteriosus showing characteristic murmur and its common variations in duration and intensity but always with late systolic crescendo into loud second sound and a diastolic diminuendo. All cases confirmed at operation.

The murmurs were high-frequency, high- or medium-amplitude vibrations, best registered at the second left intercostal space or under the left clavicle. The systolic murmur was of crescendo configuration up to the second sound in all but two instances. The latter two cases showed decrescendo systolic murmurs, one terminating in mid-systole, the other extending to the second sound. The diastolic murmurs, where present, followed the second sound immediately, in a decrescendo fashion, and consisted of lower amplitude vibrations than those of the systolic component.

CONCLUSIONS

Phonocardiographic study of the heart sounds and the murmurs in congenital heart disease has revealed several rather characteristic appearances. Careful search for these phenomena by auscultation and their occasional registration by phonocardiograms may significantly contribute to the differential diagnosis of these anomalies.

The first heart sound as a whole was well registered in all these cases.   The auriculoventricular component was frequently accentuated in patients with right ventricular hypertension (pulmonic stenosis or ventricular defect).   This was usually best observed at the apex or fourth and second left intercostal space. The semilunar component was exaggerated at the second right intercostal space in our patients with aortic stenosis—a phenomenon described in adults with aortic stenosis by Leatham.[11]   The pulmonary element of the semilunar opening was diminished or absent in the majority of all severe pulmonic stenosis cases.

The second heart sound shows a semilunar component which is the only one consistently registered in the logarithmic tracing and audible with the stethoscope.

The degree of splitting noted in this component is of great value in the differential diagnosis of the conditions discussed in this study; the most marked splitting is observed in patients with atrial septal defect (0.07 sec. or more); normal degree of splitting (0.04 sec. or less) is present in cases with ventricular defect or patent ductus arteriosus.   Pulmonic stenosis of all varieties shows either completely single semilunar components or only mild degree of splitting.   In contrast to the findings of Abrahams and Wood,[7] our data suggest an inverse relationship between the severity of pulmonic stenosis and the degree of splitting of the second sound.   Patients with aortic stenosis, as expected, also show single or narrowly split second sounds.

The intensity of the second sound, principally its semilunar component, was of considerable differential value in the analysis of our patients.   The second sound of normal infants and children is louder in the second left than in the second right intercostal space, because of the predominance of the pulmonary elements. This same relationship is preserved in the majority of atrial defects, small ventricular defects, and patent ductus arteriosus cases.   Patients with pulmonary arterial hypertension, such as is seen with large ventricular defect, single ventricle, and a large patent ductus arteriosus, usually show an exaggeration of this relationship, the pulmonary element being of much higher amplitude than is ordinarily observed.   The reverse of this situation is present in pulmonic stenosis, where because of the diminution of the pulmonary element, the second sound is commonly absent at the second left intercostal space.   Under these circumstances, frequently the aortic element is registered as a single, high-amplitude sound at the fourth left, or less commonly, at the second right intercostal space.

Systolic murmurs in this series have shown a constant diamond configuration in the stenotic lesions.   The aortic stenosis murmur is best heard at the second right intercostal space with the apex of the diamond in the first third of systole. By contrast, pulmonic stenosis, including tetralogy of Fallot, regularly is accompanied by a diamond-shaped murmur, the apex of which is in mid-systole.   Pulmonic murmurs are best audible at the left sternal border; valvular stenosis tends to be heard maximally at the second intercostal space, infundibular stenosis at the fourth intercostal space.   There are many exceptions, however, to this point in differential diagnosis.   All the systolic murmurs originating in aortic or pulmonic stenosis transmit very well to the neck and back.

A late crescendo systolic murmur, maximal at the second left intercostal space, is practically diagnostic, in our experience, of patent ductus arteriosus. We have thus far not demonstrated it in any other congential heart condition, and it has been present in all our typical patent ductus arteriosus cases, and five out of seven "atypical" ones. This murmur, like the ones already mentioned, is heard quite well in the neck.

Plateau or decrescendo type systolic murmurs were registered in our patients with septal defects. Atrial defects usually, but not invariably, cause low-amplitude murmurs that are best registered at the second left intercostal space. Ventricular defects, by contrast, are accompanied by high-amplitude murmurs with maximal intensity at the fourth left intercostal space or the xiphoid. Neither of these murmurs transmits well to the neck or the back, though the ones originating in ventricular septal defect are much louder and transmit better than those in atrial septal defect.

Diastolic murmurs, very rarely and only in the severest cases, appear in patients with pulmonic stenosis. Both early and mid-diastolic murmurs have been registered in such instances. Leatham[11] and Sprague[12] suggest that the early diastolic murmur in these cases really represents a systolic murmur, caused by the delay of right ventricular systole beyond the time of closure of the aortic valve.

Congenital aortic stenosis is rarely accompanied by a diastolic murmur. If it occurs, a rare instance indeed, it has the characteristics of aortic incompetence.

In contrast to the group of patients with stenotic lesions, the children with large left-to-right shunts very commonly exhibited a variety of diastolic murmurs.[13] Patients with atrial defects, ventricular defects, single ventricles, or patent ductus arteriosus all may show apical mid-diastolic murmurs with equal frequency. Cases with ventricular defect or a single ventricle are more likely to show presystolic apical murmurs than the rest of the left-to-right shunt group. The points in differential diagnosis between this group of presumably "functional" mitral murmurs and the group representing organic mitral stenosis have been outlined in a previous publication.[13] Early diastolic murmurs were seen most regularly in the group of patent ductus arteriosus patients, less commonly with atrial or ventricular septal defects.

SUMMARY

1. Sixty-four patients with congenital heart disease were studied by means of phonocardiography.

2. The murmurs and the valvular elements of the heart sounds are described in the common types of congenital heart diseases.

3. The value of ausculation and phonocardiography is stressed in the differential diagnosis of these conditions.

The authors would like to express their thanks to Mr. M. B. Rappaport, E. E., for much helpful advice on technique and on interpretation of tracings. We are also indebted to Dr. Howard B. Sprague and Dr. Samuel A. Levine for their helpful comments.

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INTRACARDIAC PHONOCARDIOGRAPHY

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PHONOCARDIOGRAMS are usually recorded from the chest wall but when
picked up from the esophagus, some components are obtained more clearly,
such as the auricular sound. A vibration that is perceived like the heart sound
is assumed to receive a certain amount of damping, such as absorption and
reflection, on its way from the heart to the chest wall, and is distorted to some
extent. It seemed of physiological and clinical significance to pick up the proto-
type of the heart sounds from the esophagus, or better still, from the cardiac
cavity itself, rather than from the chest wall.

It would also be of clinical interest to obtain a phonocardiogram from various
parts of the heart to which a catheter could be introduced in the case of congenital
malformation of the heart. This purpose would necessitate the use of a miniature
microphone that could be attached to the tip of a catheter, but since such a device
was unavailable, the following method was employed. A condenser microphone,
using the body as one pole and devised by Koizumi[1] and Hinohara[2] for picking
up the heart sounds from the esophagus, was adapted with some modifications.
To the tip of a plastic tubing (F8), a small metal stick (Fig. 1) was attached and
well insulated. A fine, shielded wire was used for the lead wire between the metal
stick at the tip of the catheter and the grid of the oscillator circuit. The wiring
diagram of our circuit is shown in Fig. 2. The frequency of the carrier wave is
480 kc. It was assumed that the dielectric change that must occur at the tip of
the catheter by the vibration, which is thought to be the cause of the heart
sounds, would then be transferred by frequency modulation to an oscillogram
and be perceived directly as a sound through a loud-speaker. The use of a fine
shielded wire, as lead wire, in the catheter, limited the conversion of frequency to
the tip of the catheter. By this means, it became possible to record more selec-
tively the vibration in the desired portion of the heart cavity.

By a similar method, Tomomatsu and Takasaki[3,4] obtained the slow vibra-
tion especially from the right auricle. They discussed the mechanism of venous
return with their slow vibrations.[5] Moreover, they did not use a shielded wire
for the lead in the catheter and their apparatus is said to be entirely insensible
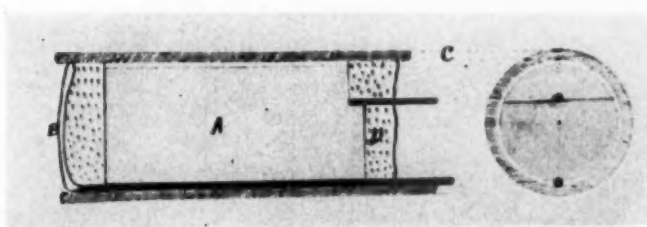to sound waves when the catheter is left in the air.[4]

Fig. 1.—The tip of the catheter.   A, Metal stick; B, Electrode of the unipolar electrocardiogram; C, Plastic tube; D, Insulator.
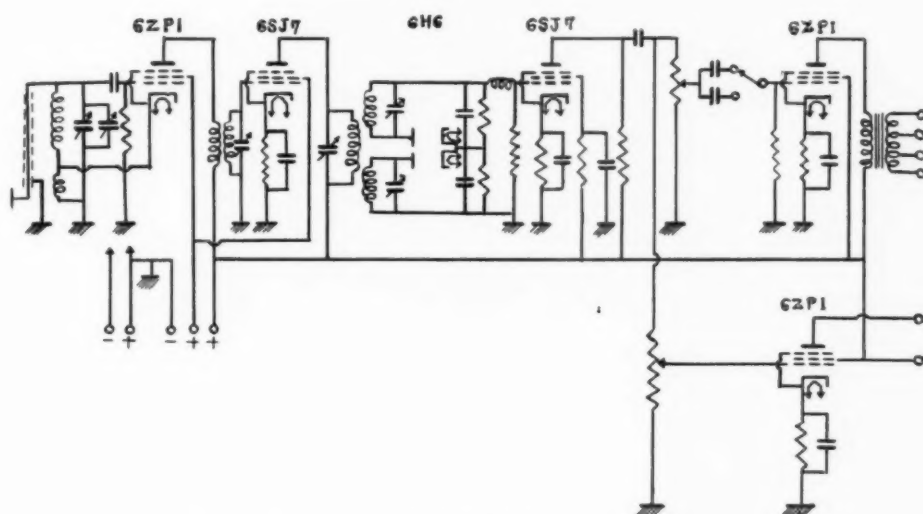

Fig. 2.—The wiring diagram of our circuit.   (Second model.)

Fig. 3.—Wave form of Japanese voiced vowel "a" articulated by an adult man.   Time: 1/100 sec.

The apparatus used in our experiment, as long as the tuning was perfect, is extremely sensitive to sound waves when the catheter is left in the air, showing that the catheter could act as an extremely small microphone which could not have been manufactured to date. An oscillogram of vowel "a", taken with our apparatus, is shown in Fig. 3.

It follows, therefore, that the apparatus and the object of research by Tomomatsu and Takasaki are a great deal different from those of our present study.

Fig. 4.—Roentgenogram of a dog, in which one catheter microphone was introduced in the left pulmonary artery and another in the left ventricle.

Under fluoroscopic observation, the catheter microphone was introduced into the heart cavity. Using over twenty adult healthy dogs, the catheter was introduced into the right heart through the cervical vein, or to the left side of the heart through the carotid artery. Venous catheterization was also carried out on three human beings, in one of which the catheter microphone reached the pulmonary artery and then heart sounds at various parts in the heart were recorded on the tape recorder.

RESULTS

Results obtained with dogs are described in the following.

1. Fig. 5, A is the recording obtained from the descending limb of the left pulmonary artery, and 5, B, that from the common pulmonary artery. Both are high-pitched murmurs of holo-

systolic phase, and the contour is oval or ellipsoidal, similar to the murmur of semilunar valve stenosis.   The time elapsed from Q of the electrocardiogram to the beginning of the murmur is 0.03 sec., shorter in 5, B than 5, A.   This means that the record obtained is that of a whirlpool of blood flow at the tip of the catheter.

2.   Fig. 6, A shows the recording obtained by contacting the tip of the catheter on the inner wall of the left ventricle by its introduction through the carotid artery, and 6, B, the recording from the chest wall made at the same time.   The former shows the auricular sound clearly.   The first sound complex of this is very similar to the first sound from the chest wall.
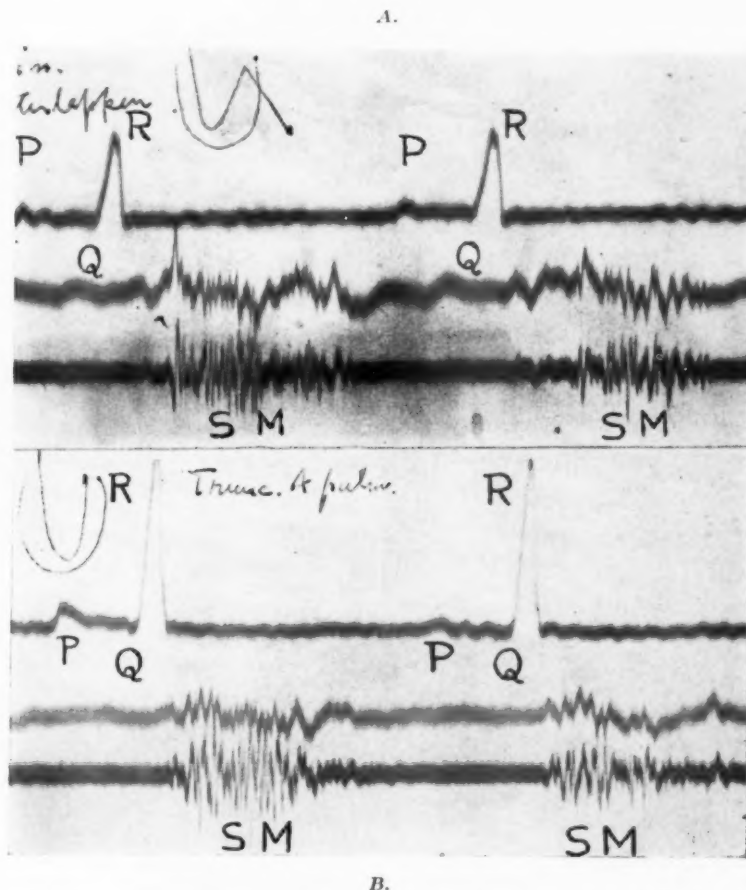
Fig. 5.—Upper tracing is electrocardiogram, middle is phonocardiogram without filter, and lower is phonocardiogram with filter.   A is the tracing from the descending limb of the left pulmonary artery, and B, from the common pulmonary artery.

3.   Fig. 7, A and B are the recordings of various points in the left ventricle of the same dog as in Fig. 6.   Presystolic ellipsoidal murmur is especially well shown in 7, A.   It is not clear whether this resulted from a temporary mitral stenosis caused by the tip of the catheter having pushed on the mitral valve, or whether such a whirlpool of blood flow exists in the left ventricle.   This presystolic murmur cannot be observed from the chest wall at the same time.

4.   Fig. 8 is the recording obtained from a point near the aortic valve in the left ventricle. It shows the auricular sound and a murmur of small amplitude that follows it.   The first sound is either prolonged or split and follows a rough systolic murmur.   The second sound is in some cases split, and a large third sound follows.

5. Fig. 9A, B, and C are records when the tip of the catheter is placed in the blood stream in the aortic arch. A holosystolic, high-pitched murmur is present, as in the case of the pulmonary artery, and it is very similar to the findings of auscultation of aortic stenosis. When the tip of the catheter is in contact with the aortic wall, the first and second sounds become more clear, as can be seen in Fig. 9, B. In this instance, this strong systolic murmur cannot be seen in the cardiograph taken from the chest wall at the same time. The whining of a dog is extremely damaging to the recording from the chest wall, but it does have as much effect on the cardiograph taken from the left ventricle or aorta. These results show that the myocardium and aortic wall exert an extreme damping effect on vibration, especially that of higher frequency.
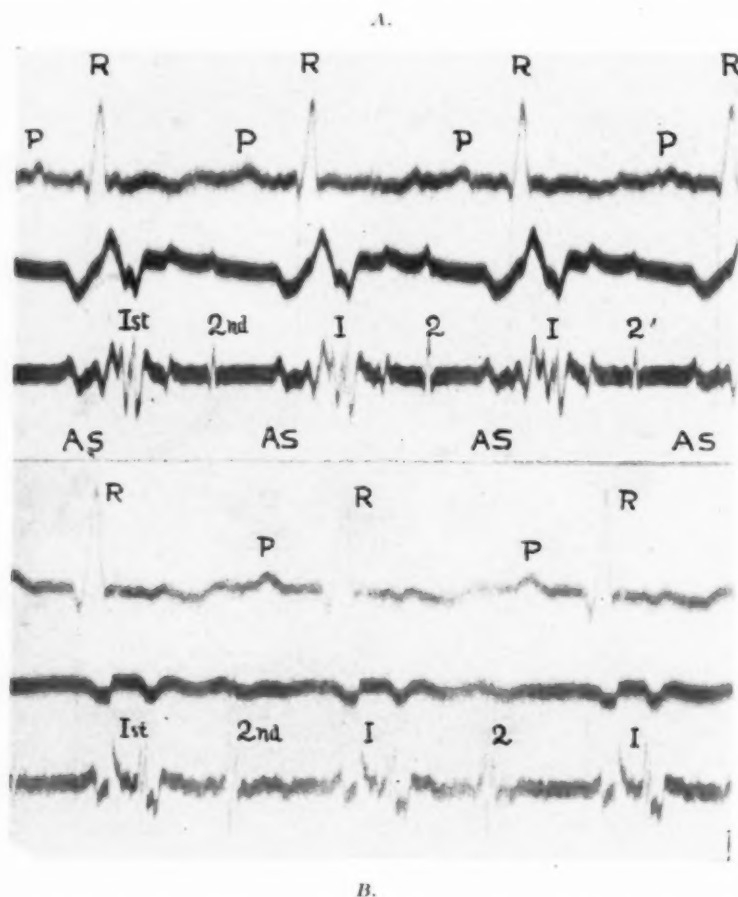
Fig. 6.—*A* is the tracing from the inner wall of the left ventricle. *B* is a tracing from the chest wall obtained at the same time as is auricular sound. Note the fluctuation of *AS-I* interval in accordance with the respiration.

SUMMARY

1. The intracardiac phonocardiography was obtained from dogs and men by means of a condenser microphone using the body as one pole.

2. Intracardiac heart sounds of men and dogs were recorded on the tape recorder.
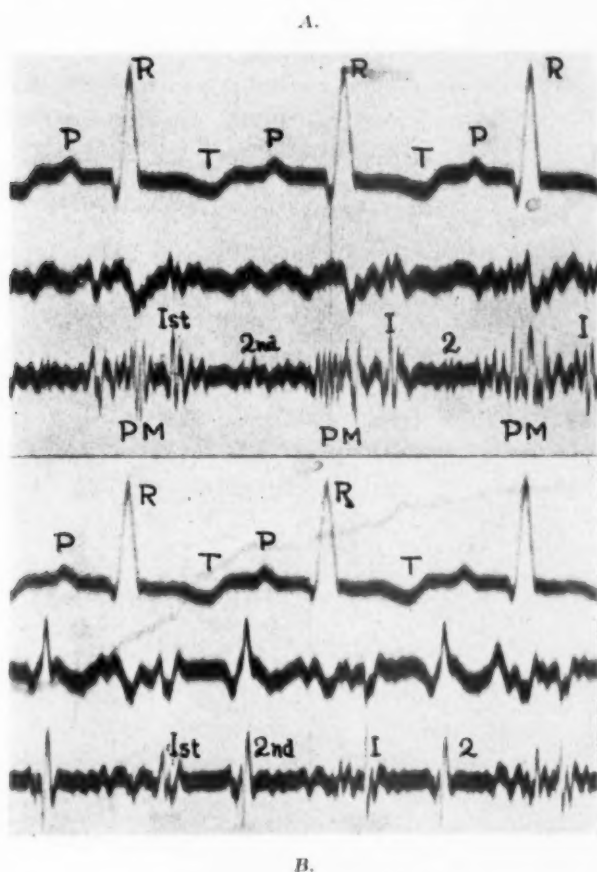
Fig. 7.—Tracings from the cavity of the left ventricle of the same dog of Fig. 6.
Note the presystolic ellipsoidal murmur.
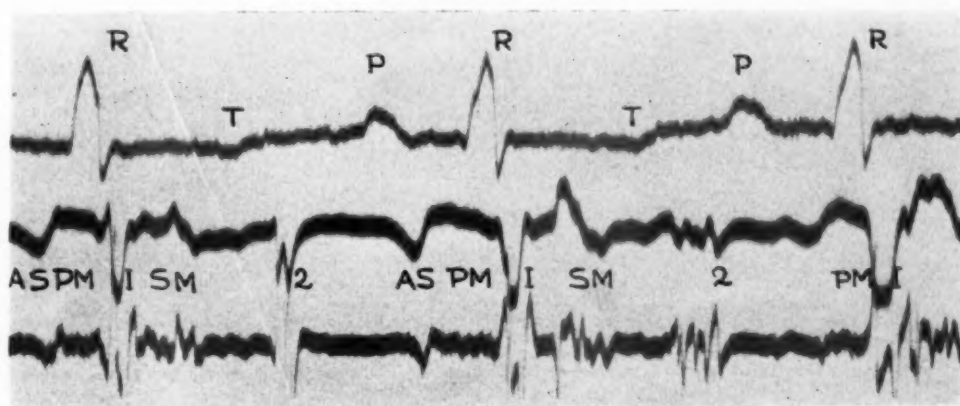
Fig. 8.—Tracing from cavity of the left ventricle near the aortic valve.

3.   The data obtained to date indicate that there exists a certain amount of blood whirlpooling inside the heart cavities and arteries.   Although this whirlpool is mostly in audible range, the damping effect of heart and arterial walls makes it impossible to hear these sounds upon the chest wall in a normal healthy person.
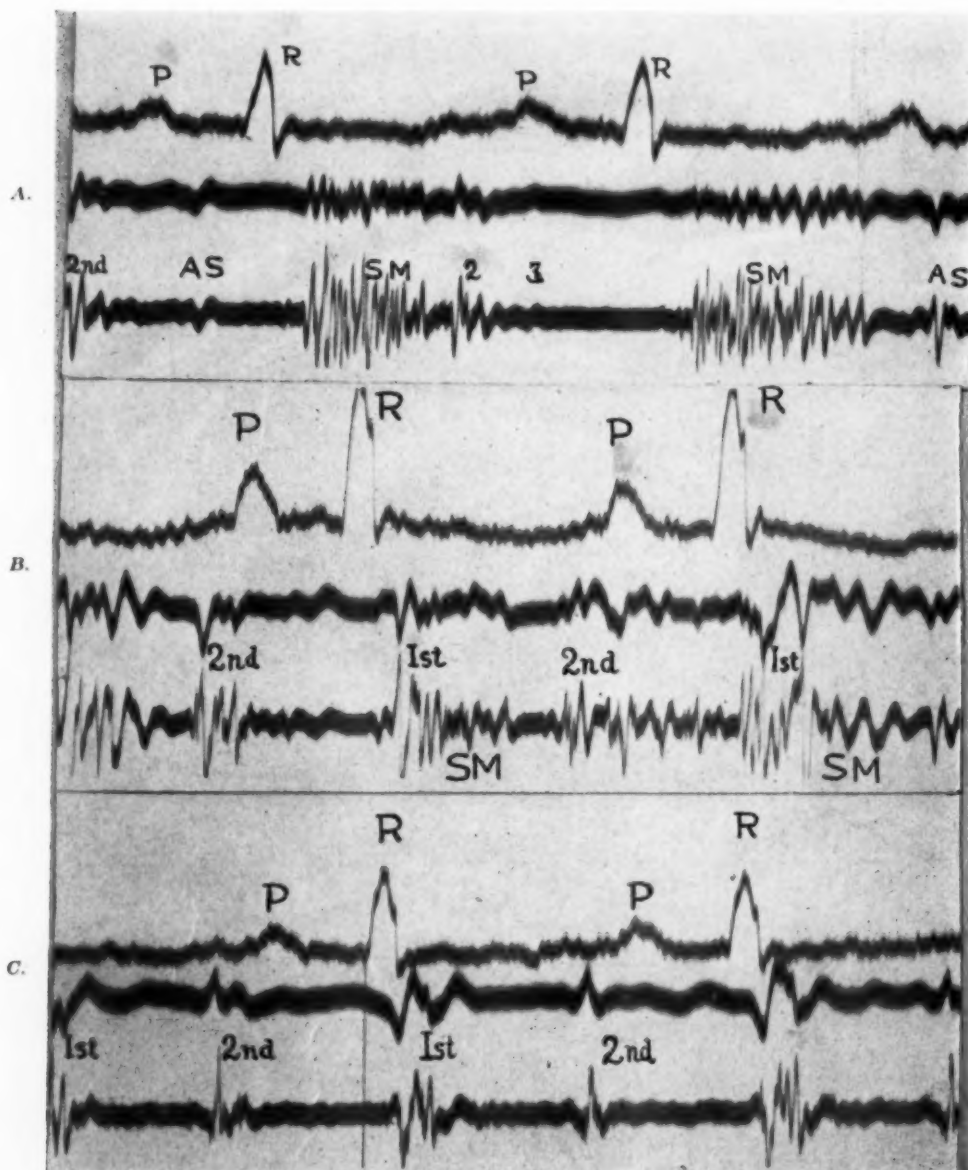
Fig. 9.—A is recording from the blood stream of the aortic arch.   B is from the inner wall of aortic arch and C from the chest wall obtained at the same time.   The whining of a dog is shown only in C.

4.   When the catheter tip is placed in the blood stream, chiefly course sounds due to a blood whirlpool are recorded, and when the tip is contacted with the inner wall of the heart, chiefly vibrations of a solid structure are recorded.   These latter are thought to be similar to the heart sounds obtained from the chest wall.

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PERFORATION OF THE INFARCTED INTER-VENTRICULAR SEPTUM

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SINCE Latham's original description in 1845 of perforation of the interventricular septum following myocardial infarction, the total number of reported cases has grown to ninety-three.[1] All but seventeen of these cases have appeared in the literature within the last 20 years. Though the clinical features of this entity have been well described, the majority of reported cases were not diagnosed until after death.

This paper will describe two cases of septal perforation following acute myocardial infarction, seen by us in the last 6 months, and a third patient who has survived for 6 years and 6 months since her infarction and septal perforation. One of us (J. C. S.) has followed our third patient since her original attack in February, 1947. Previously, the longest reported survival following perforation of the infarcted interventricular septum was 4 years and 10 months. This patient was described in 1942 by Wood and Livezey.[2]

CASE REPORTS

CASE 1.—A 68-year-old white woman, known to have moderately severe hypertension for 15 years, developed a sudden, severe substernal pain, weakness, and shortness of breath at 6 P.M. April 7, 1953. She was seen at home one hour later and found to be pale, sweaty, and dyspneic with signs of pulmonary edema. The heart size was not made out, and the heart sounds were irregular with multiple premature beats and a protodiastolic gallop heard along the lower left sternal border. No murmurs were audible. The blood pressure was 180/110 mm. Hg; the heart rate was 110 per minute. She was given morphine sulfate intravenously and sent immediately to the hospital where oxygen, morphine, and quinidine were given. At 8 A.M. the following day a Grade 4 harsh systolic murmur was audible over the entire precordium, loudest in the third and fourth intercostal spaces to the left of the sternum where a definite systolic thrill was palpable. The blood pressure had fallen to 90/65 mm. Hg. An electrocardiogram revealed deep Q waves in Leads III, aV$_F$, and right precordial leads (Fig. 1,A). There was marked elevation of S-T segments in Leads V$_1$ through V$_5$. These findings were taken to indicate an extensive acute myocardial infarction involving the interventricular septum and adjacent anterior and posterior myocardium. Because of the sudden appearance of the systolic murmur and thrill, it was felt that a perforation of the infarcted interventricular septum had occurred during the night.

This patient expired on the fourteenth day of her illness, having developed signs of right ventricular failure in addition to persistent pulmonary edema. Autopsy revealed an infarction of the apical portion of the left ventricle involving the septum, which was perforated by a two-centimeter circular defect about two centimeters above the apex. Generalized coronary atherosclerosis was present, which was most pronounced in the anterior descending branch of the left coronary artery.

CASE 2. — A 63-year-old white man was first seen in the San Diego County General Hospital on March 1, 1953, complaining of severe substernal and precordial pain since the previous day. His blood pressure had been known to be over 200 mm. Hg systolic for more than a year.   Physical examination revealed moderate cardiac enlargement, the apex being palpable in the sixth intercostal space at the anterior axillary line.   Sinus tachycardia and a multiphasic pericardial friction rub at the mitral area were present.   Blood pressure on admission was 150/90 mm. Hg.   An electrocardiogram revealed evidence of extensive infarction involving the anteroseptal and posterior myocardium (Fig. 1,B).
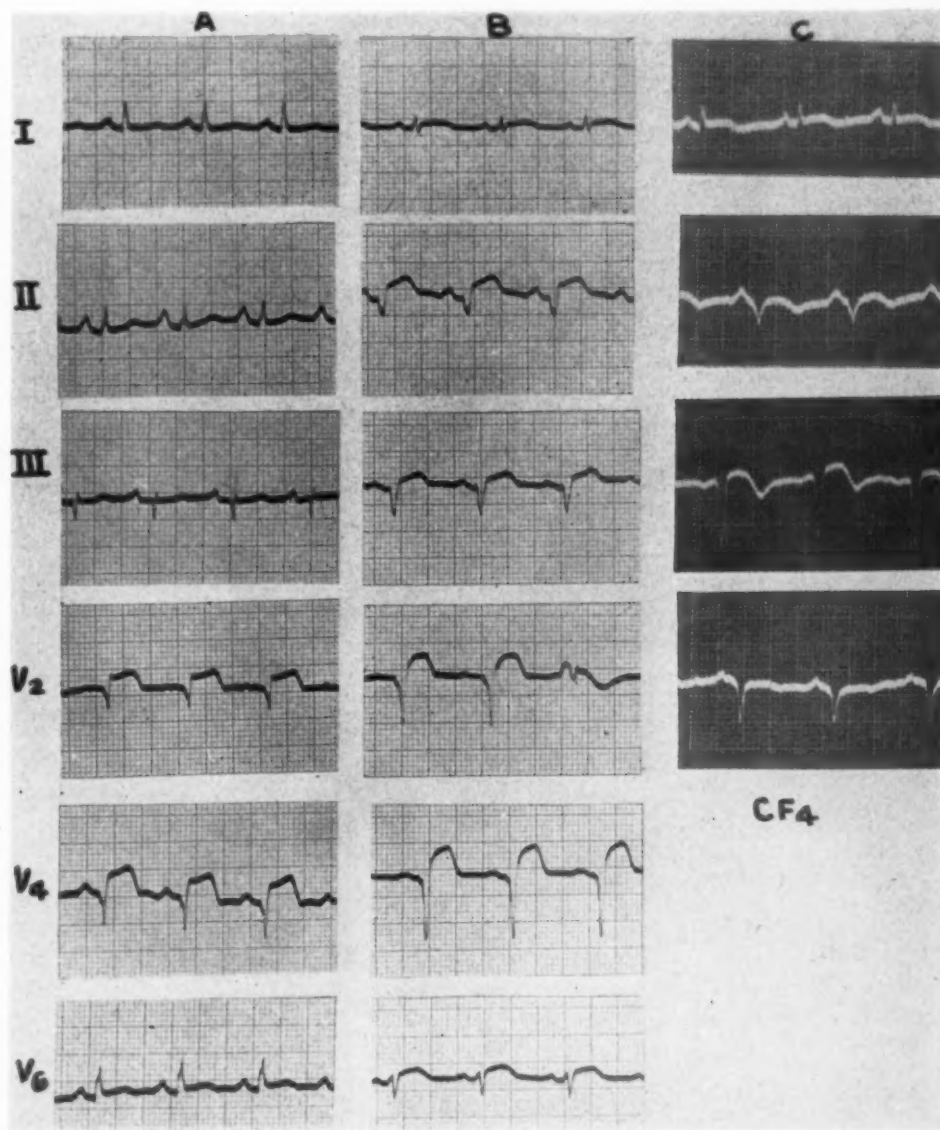

Fig. 1.—Electrocardiographic tracings of Cases 1 (A), 2 (B), and 3 (C) taken during the first week after myocardial infarction and perforation of interventricular septum.   All show simultaneously evidence of posterior infarction and acute anteroseptal infarction (Roesler-Dressler syndrome).

Treatment consisted of oxygen, morphine and Dicumarol. On the third hospital day a Grade 4 harsh systolic murmur was first noted. This murmur was heard maximally in the fourth intercostal space from the sternum to the apex, where a thrill was palpable. During the remainder of his life, this patient had intermittent substernal pain and dyspnea. He developed hepatomegaly, edema, and signs of pulmonary congestion. Death occurred 18 days after the onset of his attack. Permission for autopsy was denied. The clinical diagnosis was acute myocardial infarction involving the interventricular septum, complicated by septal perforation and congestive heart failure.

CASE 3.—A 75-year-old white woman experienced sudden substernal pain, collapse, and dyspnea on Feb 20, 1947. The past history was negative for cardiovascular disease. She was seen by one of us (J.C.S.) in her hotel room several hours after the onset of her attack and found to be in circulatory collapse. There was no discernible cardiac enlargement, and the heart sounds were of normal intensity. Cardiac murmurs were absent.

Morphine and oxygen improved her condition initially, and she was able to remain in her room under an oxygen tent during the first weeks of her illness. On Feb. 21, the day after the initial symptoms, a harsh Grade 5 systolic murmur was first heard over the entire chest, loudest in the left fourth and fifth intercostal spaces anteriorly. This murmur has remained unchanged to date and a definite thrill is palpable in its area of maximum intensity. An electrocardiogram taken on the third day of her illness revealed deep Q waves in Lead III and acute infarction pattern in Lead CF$_4$. Subsequent tracings, including unipolar leads, have confirmed the presence of extensive infarction involving the septum and adjacent anterior and posterior myocardium (Fig. 1,C).

The clinical diagnosis of this patient has been perforation of the interventricular septum secondary to myocardial infarction. Soon after the murmur and thrill appeared, edema, hepatomegaly, and ascites became prominent. The patient remained in critical condition for more than a month and has subsequently been in a state of chronic right ventricular failure. Management has consisted of a low-salt diet, ammonium chloride, and mercurial injections, at first weekly and now every 2 weeks. At present she is ambulatory, but her activity is limited to her apartment and short walks in the park nearby. She sleeps on three pillows but is comfortable most of the time. Her ankles and feet are chronically edematous, and the liver is tender and extends 3 fingerbreadths below the right costal margin. Her blood pressure is 140/80 mm. Hg.

DISCUSSION

Though post-mortem examination was possible in but one of our cases, we have felt certain of the diagnosis in the three patients presented because their findings fulfilled the classical criteria of this disorder. These criteria include evidence of acute myocardial infarction, the appearance of a harsh systolic murmur and thrill usually along the lower left sternal border within three weeks after the onset of infarction, and the sudden change in the clinical condition of the patient at the time the murmur is first noted.

All of our patients had clinical and electrocardiographic evidence of acute myocardial infarction. It is noteworthy that the electrocardiographic tracings in each case demonstrated the pattern described by Roesler and Dressler[3] as being typical of extensive septal infarction involving the anterior and posterior aspects of the heart. These authors noted in five cases showing massive septal infarction at autopsy that tracings showed simultaneously the Q_3-T_3 pattern of posterior infarction and similar changes in the right precordial leads (or lead CF$_4$ where unipolar leads were not taken) suggesting infarction of the anteroseptal myocardium as well.

In all of our cases auscultatory evidence of septal defect was absent during the initial examination after the onset of chest pain. Case 1 had been under

surveillance for a number of years because of her hypertension and had previously been without heart murmurs.   We have no knowledge of the medical history of Case 2 except that he was found to be hypertensive on a routine examination a year previous to his death.   Case 3 had been examined repeatedly during her life but had never been informed of having any abnormalities of heart or blood pressure.   The loud, harsh systolic murmur in the lower precordial region accompanied by a systolic thrill was present in each of our cases.

Simultaneous with the onset of the murmur and thrill, congestive heart failure, predominantly of the right ventricular type, developed in our three patients.   The combination of heart failure and shock seemed to cause death in Cases 1 and 2.   Sager[4] has expressed the opinion that patients with perforation do poorly because of the size and location of the infarction.   He felt that the perforation was usually of little functional significance and not responsible for circulatory failure.   However, it seems to us unlikely that the majority of these patients would develop early right ventricular failure, often with right-axis deviation, unless there were an appreciable shunt of blood from left-to-right through the perforated septum.   The change in circulatory dynamics occurs suddenly in a heart already weakened by infarction.   This situation contrasts sharply with the congenital interventricular septal defect, functioning from birth in an otherwise normal heart.   The congenital lesion is usually well tolerated for many years.

Other than a congenital interventricular septal defect, the only condition which might easily be confused with perforation of the infarcted septum is rupture of a papillary muscle secondary to myocardial infarction.   This condition is less common than septal perforation and usually results in death within a few hours. Askey[6] has pointed out that the murmur of ruptured papillary muscle occurs less commonly, is often more blowing in quality, apical in location, and sometimes both systolic and diastolic in time.   A "pseudorub" is occasionally heard in this condition, but a thrill is never palpated.   Heart failure following ruptured papillary muscle is likely to be left ventricular in type because of ensuing mitral insufficiency.

Other lesions sometimes mentioned in the differential diagnosis of septal perforation such as relative mitral insufficiency due to a dilated left ventricle, pericarditis, and rupture of the mitral chordae tendineae should offer little difficulty to the careful observer in the light of associated clinical findings.   The last-named condition is never associated with myocardial infarction.[6]

Reported studies indicate that between 7 and 9 per cent of deaths in acute myocardial infarction are due to some type of myocardial rupture.[7,8,10]   Oblath[8] has pointed out the interesting fact that among eighty patients with cardiac rupture of all types, 67 per cent of the infarctions occurred in or near the interventricular septum.   It is probable that factors responsible for septal perforation are shared by myocardial rupture in other locations as well.

According to Wessler and associates,[7] the large majority of cardiac ruptures occur between the fourth and eleventh days after infarction.   None of our cases developed this complication later than the twenty-first day.   Of Oblath's series, including eleven septal perforations, none survived more than 30 days.   The earliest septal perforation was reported by Hyman,[9] whose patient developed this complication 4 hours after the onset of symptoms of myocardial infarction.   Our

patients were first noted to have the murmur of septal defect in 14 hours, 4 days, and 3 days, respectively.

Oblath stated that rupture is three times more likely in hypertensive patients with infarction than in those with normal blood pressure, and Wessler reported hypertension in all of his patients with cardiac rupture. Rupture of the heart is rare before the age of 50.[8,10] Since myocardial infarction is predominantly a disease of men, the nearly equal distribution between the sexes of myocardial rupture would seem significant. The interesting observations of Beresford and Earl[11] and Jetter and White[12] of the high incidence of spontaneous cardiac rupture among mentally ill patients suggests that continued physical activity may be responsible for some instances of rupture following infarction.

SUMMARY

1. Three personally observed cases of perforation of the interventricular septum following myocardial infarction were presented. One of these patients has lived six years and six months after her infarction and perforation. We believe this to be longer than any previously reported survival with this disorder.

2. Criteria for the diagnosis of perforation of the infarcted interventricular septum are: (a) presence of recent myocardial infarction, (b) sudden appearance soon after infarction of a harsh systolic murmur and thrill at the lower left sternal border, and (c) the rapid worsening of the condition of the patient at the time the murmur appears.

3. The differential between this condition and rupture of the infarcted papillary muscle was discussed. This is the only condition which might easily be confused with perforation of the septum.

4. Factors thought to be contributory to myocardial rupture were presented.

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SOME ASPECTS OF SCLERODERMA HEART DISEASE

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A S IS known, scleroderma is a disease of collagenous tissue in which, besides the skin, manifold viscera including the heart can be involved. Its course can vary between a benign stationary disease and a fulminating malignancy which can appear and progress to a fatal termination in a few weeks. The malignant cases make the material of pathologists who doubtless have attributed the overwhelming part to the knowledge of scleroderma as a generalized collagenous disease. In the present era of collagenous diseases the interest of the medical world is focused on the typical autopsy cases, and the more benign forms of scleroderma have received less attention than they merit. Information on the visceral manifestations in circumscript scleroderma are scanty in the literature. Recently Pinker and Braun[1], however, have described a case of circumscript scleroderma with extensive scirrhus-like sclero-stenosis of the stomach and of the colon which preceded the onset of the skin lesions. Because every case of scleroderma can proceed to a fatal form, studies on the visceral manifestations of unselected scleroderma patients are required.

The potential heart involvement in scleroderma is of special interest because cardiac failure is a common cause of death in this disease. The heart damage in scleroderma is characterized by multifocal overgrowth of fibrous tissue with destruction of corresponding myocardial fibers resulting in multiple scars. Weiss and associates[2] were the first to ascertain "scleroderma heart disease" as a clinical and pathologic entity. They collected nine cases of diffuse scleroderma with congestive heart failure. In eight electrocardiographically studied cases, there were abnormal records. In six cases with a fatal termination, symptoms of generalized congestion were present at the time of death. In three cases the cardiac symptoms preceded the involvement of skin by two years or more. Later Mathisen and Palmer,[3] East and Oram,[4] Hurley and associates,[5] Barrit and O'Brien,[6] and the Staff of Barnes Hospital[7] have enriched the literature with six cases of scleroderma heart disease and generally confirmed the concepts of Weiss and his associates. There are no reports on the electrocardiograms of scleroderma patients collected without regard to their cardiac status. The following study was intended to present such data, keeping in mind, the difficulties of the interpretation of an electrocardiogram without histologic support.

MATERIAL

The material consists of seven cases of scleroderma with positive biopsy findings, six women and one man. These unselected patients were collected in connection with a therapeutic trial on 3-hydroxy-2-phenyl cinchoninic acid. They made the majority of the known scleroderma cases in Finland. The mean age of the patients was 27 years. No one of them presented a history of any previous disease such as rheumatic fever or other diseases known to attack the heart. No drugs affecting the electrocardiogram had been used by these patients. Besides standard and aV limb leads, multiple precordial leads of Wilson were recorded in order to reveal any focal intraventricular conduction disturbance which could be expected to be found on account of the histologic changes earlier described.[2-5]

CASE REPORTS

CASE 1.—R.L., an asthenic 14-year-old girl with diffuse scleroderma and hyperpigmentation of 8 years' duration. Sclerodactylia with limited movements and atrophic fingerpads and nails were present. A roentgenogram of the hands showed atrophy of the distal phalanges. A masklike face was observed with multiple telangiectases and unpigmented scars with retarded healing of wounds. Positive Trousseau's sign; blood calcium 10.2 mg. per 100 ml. Routine physical examination of the chest organs showed nothing abnormal. Blood pressure, 105/65 mm. Hg.

Electrocardiographic Findings.—The pulse rate was 100 per min.; slightly pointed P waves; P-R, 0.13 sec.; QRS, 0.07 sec.; Q-T, 0.36 sec.*; and relative Q-T, 0.31 sec.† No slurring or notching of QRS deflections in any of the leads (cf. Fig. 1, Case 1).

CASE 2.—R.K., an 18-year-old woman with a stationary circumscript sclerodermatous area of 9 years' duration on the right inguinal region. Routine physical examination of the chest organs revealed nothing abnormal. Blood pressure was 120/75 mm. Hg.

Electrocardiographic Findings.—The pulse rate was 88 per min.; P-R, 0.18 sec.; QRS, 0.10 sec.; Q-T, 0.36 sec.; and relative Q-T, 0.32 sec. Notching on the apical downstroke of R in Leads II, III, aV$_R$ and aV$_F$ and on the apical upstroke of S in Leads aV$_L$, V$_2$ to V$_4$, and V$_6$. The upstroke of S in Leads I and V$_5$ was slurred.

CASE 3.—V.R., a 20-year-old lumberman with extensive, now stationary, sclerodermatous skin lesions of 5 years' duration. They are located on all extremities, the trunk and head being intact. Sclerodactylia was evident. The motility of the right talocrural joint was limited, and the muscles of the lower limbs, especially those of the right leg, were somewhat atrophied. Routine physical examination of the chest organs revealed normal findings. Blood pressure was 140/85 mm. Hg.

Electrocardiographic Findings.—The pulse rate was 91 per min.; P-R, 0.19 sec.; QRS, 0.10 sec.; Q-T, 0.35 sec.; and relative Q-T, 0.31 sec. R in Lead III and S in Lead aV$_L$ showed a terminal slurring. Apex of S in Lead aV$_L$ is bifid, and R in Lead aV$_F$ notched on its basal downstroke. An r' wave is present in Leads II and V$_6$. RS-T segment is elevated in all precordial leads (cf. Fig. 1, Case 3).

CASE 4.—I.H., a 21-year-old woman with a circumscript and stationary sclerodermatous area of 7 years' duration on the left infra-orbital region. Routine physical examination of the chest organs revealed nothing abnormal. Blood pressure was 145/100 mm. Hg.

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*All measurements are made in Lead II.

†Calculated according to Ashman's logarithmic formula.

Electrocardiographic Findings.—The pulse rate was 87 per min.; P-R, 0.21 sec.; QRS, 0.12 sec.; Q-T, 0.37 sec.; and relative Q-T, 0.33 sec.   R in Leads III and V_4 and S in Lead V_1 are notched at apices.   In Lead aV_L an r' wave can be seen.   S in Leads II, III, and aV_F and the upstroke of R in Lead aV_F show a slurring.   RS-T segment is elevated in all precordial leads, and T wave is of abnormal character in Leads V_2 and V_3 (cf. Fig. 1, Case 4).

CASE 1.
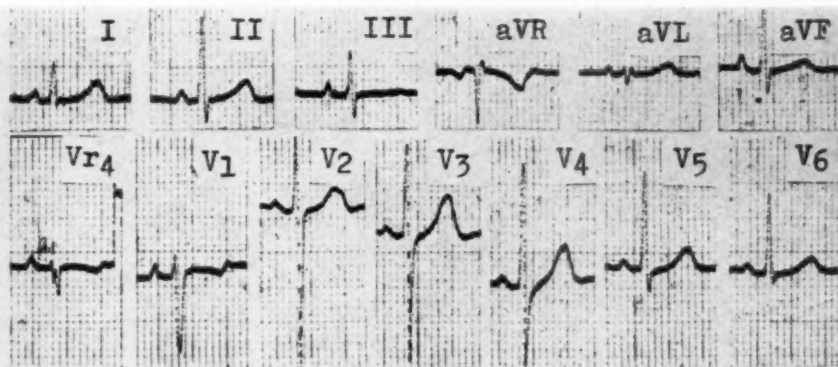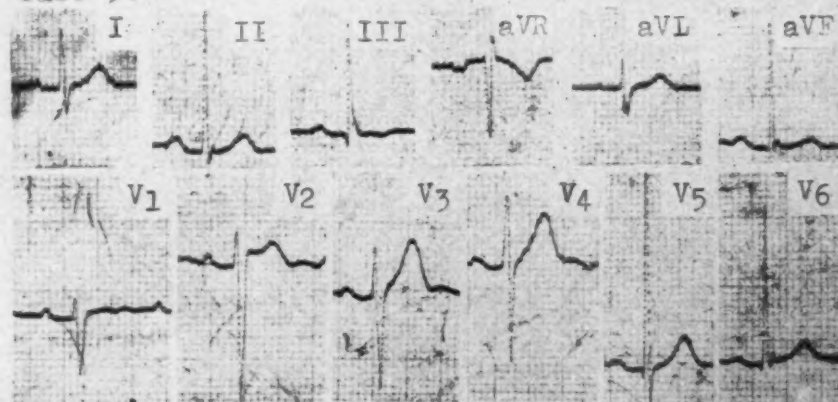
Fig. 1.—Case 1 is an example of normal record in a patient with diffuse scleroderma.   Cases 3 and 4 show electrocardiographic alterations in two patients with circumscript scleroderma.   (See case reports in text.)

CASE 5.—H.L., a 28-year-old woman with a progressive circumscript sclerodermatous area of 4 years' duration on the forehead. Since three months before admission the evening temperature was subfebrile (37.2°C. to 37.5°C.). Concurrently she had been dyspneic on exertion and slight ankle edema had occurred in the evenings. Routine physical examination of the chest organs showed normal findings. Blood pressure was 120/75 mm. Hg.

Electrocardiographic Findings.—The pulse rate was 71 per min.; P-R, 0.18 sec.; QRS, 0.11 sec.; Q-T, 0.39 sec.; and relative Q-T, 0.36 sec. T wave was bifid in Leads V_3 and V_4. No slurring or notching of QRS deflections was evident in any of the leads.

CASE 6.—A.P., a 42-year-old woman with an extensive progressive sclerodermatous area on the right elbow with a duration of six months. Routine physical examination of the chest organs revealed nothing abnormal. Blood pressure was 120/80 mm. Hg.

Electrocardiographic Findings.—The pulse rate was 83 per min.; P-R, 0.18 sec.; QRS, 0.08 sec.; Q-T, 0.40 sec.; and relative Q-T, 0.33 sec. No slurring or notching of QRS deflections was evident in any of the leads.
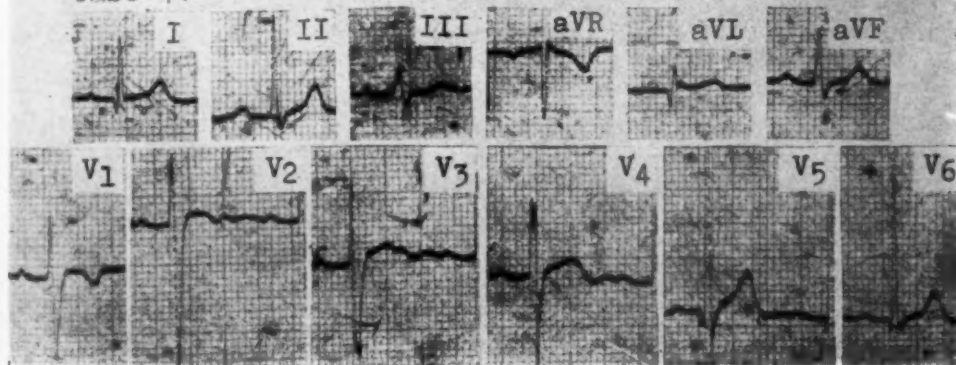
CASE 7.—S.S., a 43-year-old woman with a progressive circumscript sclerodermatous area of three months' duration on the left clavicular region. Normal findings appeared in the routine physical examination of the chest organs. Blood pressure was 140/90 mm. Hg.

Electrocardiographic Findings.—The pulse rate was 88 per min.; P-R, 0.18 sec.; QRS, 0.11 sec.; Q-T, 0.36 sec.; and relative Q-T, 0.32 sec. S in Leads I and V_3 to V_5 was slurred and prolonged. QRS from Lead Vr_1 to V_1, M-shaped; rSr'.

COMMENT

As appears from the electrocardiographic findings presented in the case reports, the P-R interval is on the upper border of normal (0.18 to 0.20 sec.) in most of these cases (Cases 2, 3, 5, 6, and 7) and prolonged (0.21 sec.) in Case 4. Only Case 1 shows an entirely normal pattern. The QRS interval is abnormally long (over 0.10 sec.) in three cases (Cases 4, 5, and 7), and Cases 2 and 3 are on the borderline (0.10 sec.). There are two cases with a normal duration of QRS complexes. Stationary slurring and notching of QRS deflections in multiple leads can be observed in four of the seven cases. Slight elevation of the RS-T segment and an abnormal configuration of the T wave in precordial leads occur in three cases. Finally, in all electrocardiograms the Q-T interval shows a relative prolongation.

DISCUSSION

It is not surprising that the electrocardiographic abnormalities presented in this paper are of a borderline character when it is taken into consideration that the material was collected on the basis of skin manifestations of scleroderma without regard to the cardiac status. On the contrary the earlier published fourteen sclerdoerma cases with electrocardiograms were selected for publication on the basis of their grave cardiac involvement. It is, therefore, natural that these evident cases of scleroderma heart disease showed more marked electrocardiographic changes such as very low amplitudes in multiple leads,[2,3,5] partial[2-5] and complete[4] heart blocks, and intraventricular or bundle branch blocks.[2] We believe that all these changes can be explained to be caused by the extensive interstitial fibrosis of the myocardium, characteristic of scleroderma heart disease. The replacement of muscle fibers by scar tissue results in the loss of functioning

units normally contributing to the total electromotive forces developed by the heart, and deflections of small amplitude appear.   In addition, the increased internal resistance of the remaining, more or less atrophied myocardial fibers, and their decreased membrane potentials, short circuited by the surrounding fibrous coat, tend to lower the amplitudes.[8]   Furthermore, the concomitantly existent polarized and depolarized areas can neutralize each other and further effect reduction in the total electric potential.   In none of our cases* were there low amplitudes in multiple leads indicating that the sclerodermatous fibrosis, if present at all, could not be very extensive.   But also a localized or patchy fibrosis can produce grave electrocardiographic alterations if it attacks the specific conducting tissue and thus can cause bundle branch system blocks.   "Depending on its location, patchy myocardial fibrosis might interfere with intraventricular conduction distal to the main bundle branches in different parts and in various layers of the free walls of the ventricles . . .   When myocardial fibrosis is extensive enough it doubltess interferes with the transmission of the activating impulse across the free wall of the ventricle, producing rapid, momentary changes in the direction of the electrical axis and momentary changes in the manifest potential differences between the right and left ventricles.   Resultant slurring and gross notching of the QRS deflections appear.   A slower rate of impulse propagation across the free ventricular wall probably accounts for the widening of QRS interval . . .   The presence of ischemic areas and regions of fibrous tissue also interferes with repolarization and produces injury currents, both resulting in abnormal S-T segment deviations and abnormal T waves."

In our opinion, these statements from the investigation of Weinberg and co-workers[9] are applicable as explanations for the slurring, notching, and prolongation of QRS complexes, and for the changes in the contour of the RS-T segment and T wave observed in many cases of the present study.   Whether these alterations actually are due to some sclerodermatous fibrotic process or to nonspecific causes remains unresolved.   The small number of our cases does not warrant any definite conclusions.   It seems, however, possible that diffuse scleroderma can exist without any electrocardiographically demonstrable cardiac involvement (cf. Fig. 1., Case 1.) and, on the other hand, in cases with scleroderma the heart can be affected even before the appearance of skin lesions, as in three cases of Weiss and associates.   Whether the heart status in scleroderma patients remains stationary or becomes progressive shall be controlled at intervals.

SUMMARY

Seven unselected cases of scleroderma were studied electrocardiographically. No marked electrocardiographic abnormalities were found.   The alterations, if present, consist of prolongation of P-R, QRS, and Q-T intervals, of slight changes in the configuration of RS-T segments and T waves, and especially of slurring and notching of QRS deflections in multiple leads.   These are interpreted as minor conduction defects possibly due to interstitial fibrosis of the myocardium.

*Except Case 8. cf. Addendum.

When this paper was in press we had an opportunity to study a new case of scleroderma, confirmed at biopsy.

CASE 8.—H.L., a 35-year-old woman with diffuse scleroderma of three years' duration. During this time the patient has been gradually exhausted and lost 26 kg. of weight. All joints have been painful and stiff, the skin overlying them being stretched and reddish. Arthraigia has been more pronounced before menstruations. The movements of the fingers have been progressively limited to semiflexion, and the face has taken a masklike appearance. In the extremities tingling sensations have alternated with numbness and painful cyanosis especially after exposure to cold. Dysphagia, dyspnea on exertion, bilateral ankle edema in the evening, and occasionally compressing retrosternal pain with impeded breath and cyanosis appeared during the last year before admission. On admission the patient was in an emaciated condition with muscular atrophy.
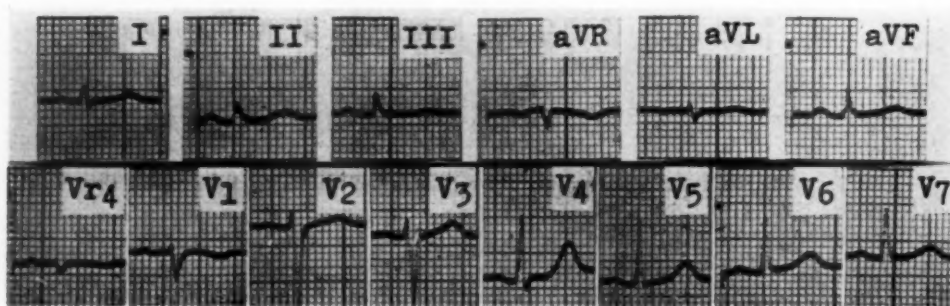
Fig. 2 (Case 8).—Tracings with low voltage QRS and moderate duration changes obtained from a patient suffering from diffuse scleroderma.

She exhibited obvious advanced changes of scleroderma with tight and shiny skin on the face and on the sclerodactylic extremities. There were increased pigmentation, interrupted by disseminated patches of vitiligo, multiple telangiectases, and retarded healing of wounds. Both feet were cyanotic and cold with some pretibial edema. Further examinations revealed somewhat loud heart sounds with good quality and without murmurs. The blood pressure was 105/75 mm. Hg, and the arm-to-tongue circulation time 12 sec. On examination of the lungs fine râles were heard basally. The white blood cell count was 11,700 with 13 per cent eosinophils. Blood calcium was 10.8 mg. per 100 ml.; sedimentation rate, 76 mm. in one hour; and antistreptolysin titer, 100. A chest roentgenogram showed prominent hilar shadows and a diffuse arborizing infiltration involving the lower two-thirds of both lung fields. The size of the heart was within upper limits of normal and its configuration normal. Examination of the esophagus revealed poor peristalsis in its distal part.

Electrocardiographic Findings.—The pulse rate was 79 per min.; P-R, 0.18 sec.; QRS, 0.12 sec.; Q-T, 0.40 sec.; and relative Q-T, 0.35 sec. Low voltage of QRS is present in multiple leads (Fig. 2).

In this case the electrocardiographic pattern reflects likely intrinsic myocardial damage, especially, when low voltage of QRS is associated with other electrocardiographic alterations' (borderline P-R, QRS and Q-T prolonged). See Discussion.

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PRESUBCLAVIAN COARCTATION OF THE AORTA

REPORT OF A CASE WITH ANEURYSM OF THE DESCENDING THORACIC AORTA AND BICUSPID PULMONARY VALVE COMPLICATED BY PREGNANCY

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W ITH recent surgical advances, coarctation of the aorta has become a practical diagnostic and therapeutic problem in the living patient. Pathologic findings must be viewed for clinical reflections. "Not only is it important," according to Hines,[1] "for the clinician to make a correct diagnosis of coarctation early, he must be able to recognize significant variations, secondary changes, complications, and associated cardiac and vascular anomalies." In the light of this statement, the following case of coarctation of the aorta is reported for these special features: The aortic narrowing originated proximal to the left subclavian artery. A large saccular aneurysm involved the descending thoracic aorta. Bicuspid pulmonary valve accompanied the coarctation. The cardiovascular lesion was complicated by pregnancy.

CASE REPORT

M. T. (482102), a 33-year-old white woman, was admitted for mental confusion to the Edward J. Meyer Memorial Hospital. She died six weeks later.

At the age of 27 years, the patient showed a blood pressure of 210/100 mm. Hg. Cardiac murmurs were heard at apex and aortic areas. Roentgenographic film of the chest revealed an aneurysm of the descending thoracic aorta.

In the six months before admission to the Edward J. Meyer Memorial Hospital, the patient was seen in two other hospitals for dyspnea and tightness in the chest with the following findings: precordial systolic murmur and thrill; systolic murmur in posterior part of left side of chest; mediastinal mass thought to be lymphoblastoma, for which treatment was given; blood pressure: right arm, systolic 146 to 175 mm. Hg; diastolic 84 to 120 mm.; left arm, systolic 94 to 130 mm. Hg: diastolic 80 mm.; right leg, systolic 110 to 114 mm. Hg; diastolic 90 mm.; left leg, systolic 112 to 120 mm. Hg, diastolic 92 mm.; pregnancy with premature delivery of a stillborn macerated fetus at 6 to 7 months; left pleural effusion and mental disturbance.

At the Edward J. Meyer Memorial Hospital, the clinical picture was that of mental confusion and progressive cardiac decompensation with murmur, thrill, and blood pressure readings as noted in the other hospitals. The radial pulse was strong in the right arm and feeble to absent in the left. The blood Wassermann test for syphilis was negative. Roentgenographic film of the chest showed a large rounded density extending upward from the base of the heart and protruding well into upper portion of left side of thorax. The density was larger than that on the film taken when the patient was 27 years old.

The clinical and roentgenologic diagnosis was psychosis—post-partum state; atypical coarctation of aorta with aneurysm of aorta; involvement of left subclavian artery.

The autopsy diagnoses were presubclavian coarctation of aorta with involvement of left subclavian orifice; abnormal position of left subclavian artery; sclerotic (hemotraumatic) aneurysm of descending aorta with rupture into left lung; flattening of thoracic vertebrae; bicuspid pulmonary valve; fibrous obliteration of ductus arteriosus; dilatation of right internal mammary artery; slight hypertrophy of left ventricle; bilateral hydrothorax; ascites; edema of legs; congestion with hemorrhage of lungs; small pulmonary thrombo-emboli; congestion of liver and spleen.

Description of Aortic and Pulmonary Lesions.—The ascending aorta and great vessels on the right side of the arch were not remarkable. The left common carotid artery, thickened by atheromatosis, measured 2.1 cm. in circumference. The distance from the orifice of the left common carotid artery to the orifice of the left subclavian artery was 2.1 cm. At a point 1.8 cm. from the common carotid artery, the aorta was narrowed to an opening 0.7×0.4 cm. The narrowing was caused by a ridge encircling the aorta; the narrowing extended for a distance of 0.4 cm. The orifice of the left subclavian artery lay between the proximal and distal edges of the narrowing. It was small, 0.8×0.2 cm. The left subclavian artery was three-fourths the size of the right subclavian artery. The ductus arteriosus was a fibrous obliterated cord which was inserted into aorta at the site of narrowing.

Just distal to the aortic narrowing, the descending thoracic aorta showed a saccular aneurysm, 13 cm. in length and 10 cm. in mid-diameter. The wall was 0.3 to 0.5 cm. thick. The aneurysm projected to the left. Its lumen contained adherent thrombus. The internal surface was rough with scattered atheromas. The aorta below the diaphragm was not dilated. The ribs were not grooved. The pulmonary valve measured 6 cm. It consisted of two cusps: one 4 cm., the other 2 cm. Both were thin and flexible. The small cusp was reticulated on the inner surface without fenestration. The large cusp, in position of normal right and left cusps, revealed, in the mid-portion of its sinus, a small raphe 0.15×0.25 cm. but no septum extending upward to the free border of the cusp.

Microscopically, the arch of the aorta revealed slight atherosclerosis and slight medial chromatropic change. At the coarctation there was marked intimal thickening with protrusion of fibrous-elastic tissue into the lumen. The adventitia was fibrosed. In some areas of the aneurysmal wall no media remained; the wall was composed of fibrous tissue. In other areas, the media were thin with remnants of fragmented elastic fibers. The most distal portion of the aneurysmal wall was involved by marked atherosclerosis, medial elastic destruction, vascularization and scarring; the aneurysm also showed recent and older thrombosis and hemorrhage.

DISCUSSION

In discussing this case, four special features will be considered:

1. *Presubclavian Coarctation.*—In the usual type of coarctation the narrowing is localized at or just distal to the insertion of the obliterated ductus arteriosus, below the orifice of the left subclavian artery. Our case exemplifies a presubclavian coarctation involving the orifice of an abnormally placed, narrow subclavian artery.

In Hamilton and Abbott's[2] review of 200 autopsied cases of coarctation of the aorta beyond infancy (reported from 1791 to 1928) only four cases were found with presubclavian narrowing. Reifenstein and associates[3] in their review of 104 autopsied cases above 2 years of age (reported from 1928 to 1947) listed two references to presubclavian coarctation. Additional cases beyond infancy with pathologic proof were reported by Umber,[4] Bini,[5] Lenègre and de Brux,[6] Bing and associates.[7] An abnormal left subclavian artery—in position and caliber— with involvement of its orifice by the aortic narrowing frequently accompanied presubclavian coarctation.

The clinical picture of presubclavian coarctation with or without an abnormal subclavian orifice or artery differs from that in the usual type of coarctation in several respects. Our case demonstrates hypotension of the left arm, diminished volume of left pulse, and absence of erosion of ribs. According to reported cases the left shoulder and arm may be cool, pale, and underdeveloped. If eroded ribs are present, they are seen only on the right side. Surgically, use of the left subclavian artery is precluded in reconstruction. Physiologically, direct intra-arterial pressure and blood flow tests yield diagnostic information.

In one case[7] the clinical picture of presubclavian coarctation was proved at operation. In only three cases[8,9] other than ours was clinicopathologic coarctation made through autopsy. Bremer[10] discussed the embryologic basis of presubclavian coarctation with variations in position of left subclavian artery
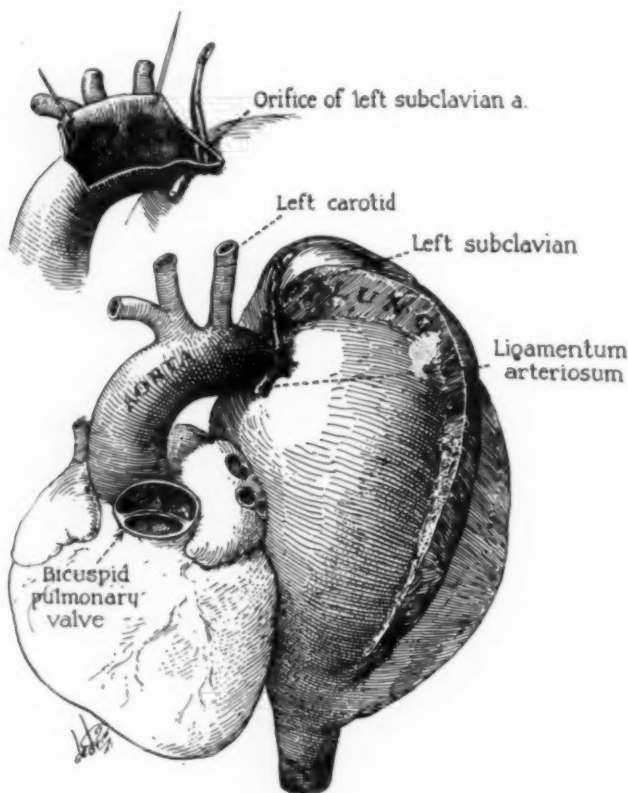
Fig. 1.—Presubclavian coarctation of aorta with aneurysm of descending thoracic aorta and bicuspid pulmonary valve.

II. *Aneurysm of Descending Thoracic Aorta.*—True aneurysms of the aorta distal to coarctation are not well known. Hamilton and Abbott[11] cited seven cases of the lesion which we find acceptable. Reifenstein and associates[3] described one personal case and had references in their bibliography to fifteen cases.[12] Adding fourteen cases[5,6,13-17] including our own, thirty-six cases are presented of

apparently true distal aneurysm (exclusive of simple dilatation, dissecting aneurysm and false aneurysm), with all but one in the descending thoracic aorta.

The thirty-six cases can be briefly analyzed. The ages of the patients ranged from 8½ years to 54 years. Twenty-three patients were between 10 and 30 years of age. The sex was male in twenty-three patients and female in thirteen patients. In sixteen cases roentgenographic examination of the thorax revealed a mass, frequently diagnosed as aneurysm. The mass was generally spherical, continuous with the aorta, on the left side, and in the posterior mediastinum. Occasionally masses showed calcification. Aneurysms were usually single, fusiform, or saccular. As a rule several centimeters in diameter, they varied from cherry to fetal-head size. Thrombosis of the lumen and erosion of the spine were found. Perforation into left bronchus, esophagus, left lung, left pleural cavity or mediastinum with hemorrhage was a common cause of death.

From an etiologic and pathogenetic standpoint, the aneurysms reported in the descending thoracic aorta were classified chiefly: mycotic, healed mycotic, or sclerotic. It would seem that the answer to the development of sclerotic aneurysms requires consideration, not just of morphologic changes, but also of physiologic alterations in the aorta distal to coarctation. Morphologically, the aorta, below the coarctation in many cases manifests productive or regressive changes[3,18] which may be interpreted as responses to trauma. The trauma may represent the hemodynamic effect of jets, eddies, or turbulence arising from the great velocity of flow developed by blood passing through the coarctation.[19] Further, Abbott postulated the influx of returned blood from the three upper aortic intercostal arteries as a weakening factor to the aortic wall. Whether a true aneurysm occurs may depend on the relationship of the intraluminal forces to the mural changes. In direct measurement[20] of the blood pressure in the aorta distal to coarctation, the diastolic pressure is of sufficient magnitude to contribute a sizable expanding force for aneurysm formation. We consider so-called sclerotic aneurysms of the descending thoracic aorta in coarctation, then, as "hemodynamic" or "hemotraumatic" aneurysms.

Our case of distal aneurysm is of particular interest for several reasons. Blood returning from the intercostal arteries could not have played a pathogenetic role because prominent collateral circulation was not found and because the orifices of the intercostal arteries were blocked by thrombosis in the aneurysm. We have found only two other distal aneurysms in presubclavian coarctation.[5,6] The aneurysm in our case was known to have existed for at least 6 years during which time it enlarged measurably. In size, the aneurysm is one of the largest recorded. Clinically, it was suspected twice to be a lymphoblastoma for which roentgenographic treatment was given.

III. *Bicuspid Pulmonary Valve.*—In respect to the combination of bicuspid pulmonary valve with coarctation our case may be unique for we find no reference to the combination in several reviews.[2,3,21,22] The bicuspid pulmonary valve had no clinical significance; it could be accepted as congential in origin.

IV. *Pregnancy as a Complication.*—In our patient pregnancy had a deleterious effect on the course of the coarctation. Between the second and third

trimester, it started the patient (after 33 years of comfortable life with her anomaly) on a progressive downhill course to death. Reports[23] in the literature stress the high mortality rate of coarctation to the woman and fetus in pregnancy and at parturition. There is also a high incidence of maternal morbidity post partum.

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STUDIES OF QUINIDINE PLASMA LEVELS AND RATE OF DECLINE FOLLOWING CESSATION OF QUINIDINE ADMINISTRATION

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THE usefulness of quinidine in the management of cardiac arrhythmias has been enhanced by the better understanding of dosage based on plasma level studies.[1-3] Quinidine is most often used in patients with heart disease. It is, therefore, of importance to know whether individuals with heart disease excrete or destroy quinidine in an abnormal manner. It has been suggested by Brown and associates[4] that patients in congestive failure maintain blood levels of quinidine for longer periods than normal persons and that toxic reactions from overdosage are likely unless this factor is considered in planning treatment.

It was the purpose of this study to determine the magnitude of the difference in quinidine blood levels of cardiac patients and normal individuals during and after drug administration and to ascertain whether or not dysfunction of the kidneys or the liver is involved.

MATERIAL AND METHODS

Plasma quinidine levels were determined in duplicate by the fluorometric method of Brodie and Udenfriend,[5] using a Coleman photofluorometer. The specificity of this method has been investigated by Linenthal and associates.[6] No drug known to be capable of interfering with this method of quinidine level determination was given. In this laboratory the experimental error was calculated on the basis of repeated determinations on identical samples, and on the basis of known dilutions, and found to be ±0.2 Gm. per liter.

Four groups of individuals were studied:

1. The healthy control group consisted of eighteen men with no evidence of any systemic disease. Hospital employees and young ward patients recovered from minor illnesses constituted this group.

2. Group of cardiac patients. Twenty-four men with rheumatic, syphylitic or arteriosclerotic heart disease (Functional Class 4, American Heart Assoc.) and congestive failure were studied. They were hospitalized, placed at bed rest, and compensated as well as possible by means of mercurial diuretics, digitalis, and xanthines, prior to the administration of quinidine.

3. Group of patients with liver disease. Eighteen men with either infectious hepatitis or Laennec's cirrhosis were studied during the acute phase of jaundice. All patients had obvious liver disease with appropriate history and clinical findings, and had icteric indices of 20 or more, and abnormal cephalin flocculation and/or thymol turbidity tests at the time of quinidine administration.

4. This group of patients with renal disease consisted of sixteen men with either glomerulonephritis or prostatic obstruction to the urethra. All individuals had renal failure, manifested by a blood-nonprotein nitrogen greater than 70 mg. per cent and creatinine greater than 3.0 mg. per cent at the time of quinidine administration. Any uremic patients with a detectable component of heart disease were deliberately excluded.

Each of these seventy-four individuals was placed on the following routine. Quinidine sulfate, 0.4 Gm., was given at 7 A.M., 12 noon, 4 P.M., and 8 P.M. for nine doses or forty-eight hours. Approximately two hours after the last morning dose, venous blood was drawn for a peak level determination. Blood levels were repeated every 24 hours until no quinidine could be found, i.e., 2, 26, and 50 hours after the last dose.

This experiment was planned to: (1) determine the peak plasma quinidine level reached on this dosage schedule, (2) analyze the rate at which the body in equilibrium with a known quantity of quinidine removed the drug from the blood stream, and (3) note whether the presence of cardiac, hepatic, or renal failure altered either of the first two determinations.

All means were subjected to routine statistical analysis,[7] with calculation of the group means, their standard deviation, and standard error. A difference between means exceeding twice the Standard Error of the Difference between two means was considered significant.

<center>RESULTS</center>

Each of the four groups had approximately the same mean peak quinidine level of 4.1 mg. per liter (Table I). Twenty-six hours after cessation of quinidine administration the group of normal persons and of jaundiced and uremic patients had quinidine levels of the same order (1.4 mg. per liter) and about 65 per cent lower than the observed maximum. The group of cardiac patients had a mean blood quinidine level of 2.10 mg. per liter, a decrease of only 49 per cent, and this figure of 2.1 is significantly higher than the normal control group mean. The standard deviation of the cardiac group (1.4 mg. per liter) was much larger than that of the other groups and indicates the greater variability in the rate of decline of blood levels in cardiac patients.

At 50 hours the blood of normal persons and of jaundiced and uremic patients had declined to a very low level (0.05 to 0.18 and 0.2 mg. per liter, respectively). Again the rate of decline in the cardiac group was persistently slower and the mean quinidine level was approximately six times higher than the normal control group. The quinidine levels of the jaundiced and uremic groups at 26 and 50 hours were not significantly different from those of the normal control group.

TABLE I. SERIAL PLASMA QUINIDINE LEVELS

GROUP	NUMBER	HOURS AFTER LAST ORAL DOSE		
		2 HOURS	26 HOURS	50 HOURS
Control patients	18	4.13 mg./L.	1.328 (M_1)	0.052 (M_2)
		±0.22	±0.6	±0.16
Number		18	18	6
Heart failure patients	24	4.2	2.10 (M_3)	0.39 (M_4)
S.D.		±1.6	±1.4	±0.74
S.E. (M_1-M_3)		—	±0.33	—
S.E. (M_2-M_4)		—	—	±0.16
Number		24	24	13
Liver failure patients	18	4.1	1.64 (M_5)	0.18 (M_6)
S.D.		±0.27	±0.8	±0.7
S.E. (M_1-M_6)		—	±0.2	—
Number		18	17	10
Kidney failure patients	16	4.2	1.2 (M_7)	0.2 (M_8)
S.D.		±0.28	±0.24	±0.27
S.E. (M_1-M_7)		—	±0.15	—
Number		16	16	7

DISCUSSION

The rate of decline of plasma quinidine levels following cessation of administration is less rapid in cardiac patients with congestive failure than in either normal persons or patients with frank liver or kidney disease. By studying the rate of decline from a measured plasma level, the factor of absorption was eliminated.

There is no evidence in the present experiment that either hepatic or renal failure was responsible for the higher levels observed in cardiac patients. These organs are the principal routes for quinidine excretion. It does not seem likely, then, that hepatic and renal changes secondary to cardiac failure are the factors responsible for this slower loss of quinidine from the blood of cardiac patients. A tendency for hypertrophied cardiac muscle to selectively retain previously absorbed quinidine and hence to release it slowly may be a factor.[8]

This slowly declining level of quinidine in the blood of cardiac patients is not a factor of slower excretion and thus does not result in a more pronounced cumulative effect in such patients. The blood levels of quinidine reached on a standard dosage were the same in the normal, cardiac, renal, and hepatic groups. Development of serious cardiac arrythmias such as ventricular tachycardia should not be attributed to an unforeseen cumulation of quinidine in the blood of a cardiac patient. This failure of cardiac patients to develop unusually high blood levels of quinidine on prolonged therapy has been noted previously.[1]

Serial determination of blood quinidine levels following cessation of administration also revealed a significant residue of quinidine in nearly all persons at 26 hours and in many persons 50 hours afterwards. Such a persistence of quinidine in the blood is in accord with numerous previous observations[1,9] in both normal and cardiac patients.

SUMMARY

1.   Quinidine sulfate was administered in divided dosages for forty-eight hours.   Serial plasma quinidine levels were measured 2 hours, 26 hours, and 50 hours after the last dosage.   Four groups were studied: normal individuals, and patients with obvious heart, renal, and hepatic disease.

2.   Individuals with cardiac disease exhibited a slower decline of quinidine level than the other three groups.

3.   The peak levels reached by all the groups were the same.

4.   Significant levels of quinidine persisted in the blood of all individuals for 26 hours, in many for 50 hours.

5.   The slower loss of quinidine from the blood of cardiac patients is not thought to be a function of delayed excretion by liver or kidneys and does not carry with it the threat of excessive cumulation in the blood of these patients.

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STAPHYLOCOCCUS ENDOCARDITIS

A Report of Three Cured Cases

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THERAPY in cases of staphylococcus endocarditis is often difficult for several reasons. The fulminant course of staphylococcus endocarditis requires treatment that must usually be prompt if it is to be effective. Penicillin resistant strains are common and the incidence of such strains appears to be increasing.[1-6] In addition, an initially sensitive organism may develop increasing resistance to penicillin as well as to other antibiotics being used.

At the present time, there is only limited data available on the efficacy of the newer antibiotics in cases of staphylococcus endocarditis. For this reason, we are presenting our observations on three cases of hemolytic *Staphylococcus aureus* endocarditis seen at this hospital during the past three years.

CASE REPORTS

CASE 1.—A 19-year-old Negro soldier was apparently well until the morning of April 10, 1950, when he developed a headache, chills, and fever. He entered the hospital where he was found to have a gonorrheal urethral discharge. Sulfadiazine medication cleared the gonorrhea completely within two days. During his first night in the hospital his temperature rose to 105°F. (Fig. 1). A loud, harsh apical systolic cardiac murmur was heard at this time. The physician noted numerous scars on the patient's skin in both antecubital areas, whereupon the patient admitted that he had been taking heroin intravenously for many months. Although he gave no history of having had rheumatic fever, the patient had been told at the age of ten years that he had a heart murmur. On April 12, he developed severe cramping abdominal pain, with nausea, vomiting, diarrhea, and generalized weakness.

Blood cultures taken on April 11 and 13 showed profuse growth of hemolytic *Staphylococcus aureus* in 48 hours. On April 14, he was given 100,000 units of penicillin every two hours. This was increased the following day to a total dose of 2 million units daily. On April 15, he developed petechiae of his hands and feet as well as a stiff neck. The cerebrospinal fluid showed no increase in cells; protein was 98 mg. per cent, and cultures were negative. On April 15, he was started on 0.5 Gm. aureomycin every six hours and 0.25 Gm. streptomycin every four hours. The streptomycin was discontinued on April 18. On April 21, the penicillin dose was increased to 2.4 million units daily and on April 29 further increased to 4.8 million units. Throughout this period the patient remained acutely ill. On April 19, his right elbow was painful, warm, and swollen, but this cleared completely by April 25. A blood culture on April 20 produced salt-resistant, mannite fermenting hemolytic *Staphylococcus aureus*. This organism was sensitive to 0.015 unit of penicillin per c.c., to 8 μg streptomycin per c.c., and to less than 5 μg aureomycin per c.c. On May 8, the patient developed pain in the left upper quadrant of the abdomen and in the left chest with a pleural friction rub. He was transferred to this hospital on May 10, 1950.

On admission to Letterman Army Hospital, the patient's temperature was 103°F.; pulse, 118; and blood pressure, 110/68 mm. Hg. He appeared both acutely and chronically ill and had marked malaise and generalized weakness. A loud harsh systolic murmur was audible over the entire precordium but was maximal in the mitral area. His abdomen was diffusely tender with greatest tenderness in the left upper quadrant. The spleen could not be felt. No petechiae were present.

Laboratory findings: At the time of admission to the hospital, the leucocyte count was 26,700, and the erythrocyte count 3.62 million. The hemoglobin was 10.9 Gm., and the corrected erythrocyte sedimentation rate (Wintrobe) was 16 mm. per hour. Urinalysis showed one-plus albumin and 30 to 50 white blood cells per high-power field. The Kahn test was negative. The blood nonprotein nitrogen was 31 mg. per cent. His electrocardiograms revealed nonspecific ST-T wave abnormalities in the precordial leads. A roentgenogram of the chest showed moderate cardiac enlargement with normal lung fields.
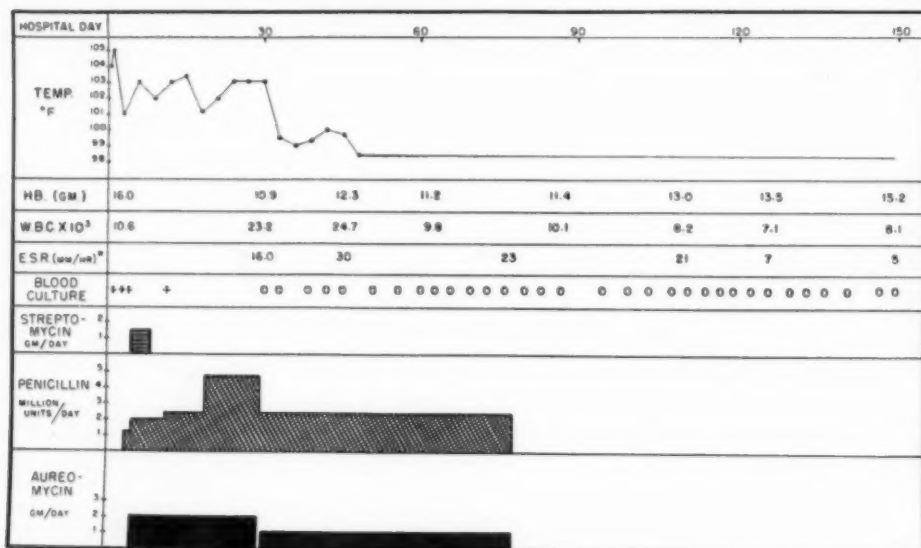
Fig. 1.—Clinical course of a patient (Case 1) with hemolytic *Staphylococcus aureus* who responded favorably to combined penicillin and aureomycin therapy. *Wintrobe.

Hospital course: The patient was maintained on 1.0 Gm. aureomycin and 2.4 million units of penicillin daily, but for two weeks after admission he remained acutely ill. On May 23, the leucocyte count was 24,700, and the corrected erythrocyte sedimentation rate 30 mm. per hour. His temperature, white blood cell count, and sedimentation rate gradually returned to normal, and all blood cultures taken were negative. Steady clinical improvement was observed, and on June 20 he began ambulation. He had received penicillin for 75 days and aureomycin for 73 days when these medications were discontinued on June 28. After two weeks of ward ambulation, the patient developed marked shortness of breath and an enlarged tender liver. He was then digitalized and placed on a low-sodium diet which resulted in marked improvement. He was discharged from the hospital on Sept. 28, 1950 at which time he was asymptomatic except for moderate exertional dyspnea.

CASE 2.—A 22-year-old man was normally active until he began to have bouts of dyspnea, weakness, and precordial pain during strenuous basic training exercises. He was admitted to an Army hospital for these complaints on Feb. 26, 1951. As a child he had chorea with no apparent rheumatic residuum ever having been noted. Two months prior to admission he had a tooth extracted without the administration of antibiotics. At the time of hospitalization there was

clubbing of the fingers, cardiac enlargement, and systolic and diastolic murmurs were heard over the aortic area. On March 2, 1951, he developed pain and swelling in the left popliteal area. Hemolytic *Staphylococcus aureus* grew out of blood cultures obtained on March 17 and 18. Sensitivity tests showed that there was practically no inhibition of the cultured organism by 15 units of penicillin per c.c., and it was highly resistant to streptomycin. Nevertheless, 2 million units of crystalline penicillin were given intramuscularly every three hours until the patient was transferred to this hospital on March 21 (Fig. 2).

On admission, the patient appeared chronically ill with marked weakness, pallor, and emaciation. His rectal temperature was 98.2°F.; the pulse rate, 80; and blood pressure 130/0 mm. Hg. Bounding femoral and radial artery pulsations were present, but the left posterior tibial artery pulsations were absent and the left dorsalis pedis pulsations were diminished. Clubbing of the fingers was marked. There were no petechiae or subungual splinter hemorrhages. There was a tender, pulsating, eggsized mass in the left popliteal fossa. The lungs were normal on examination. The heart was enlarged to the left; a loud systolic murmur and a long blowing diastolic murmur were heard at the aortic area. The physical examination was otherwise normal.

Laboratory findings: The leucocyte count was 9,100; the hemoglobin was 7.8 Gm.; the hematocrit, 25 per cent; the corrected erythrocyte sedimentation rate, 19 mm. per hour (Wintrobe). A urine specimen had a specific gravity of 1.024, a trace of albumin, and 5 to 10 red blood cells per high-power field. The serologic test for syphilis was negative. The blood nonprotein nitrogen was 18 mg. per cent. Roentgenograms of the chest revealed normal lung fields and generalized cardiac enlargement, particularly involving the left ventricle. The electrocardiogram was abnormal because of nonspecific ST-T changes.

Hospital course: On March 23, penicillin therapy (which had been discontinued for two days) was recommenced. Two million units were given intramuscularly every three hours. Carinamide administration was started on March 29. A left femoral arteriogram performed on April 20 demonstrated a large aneurysmal sac at the bifurcation of the popliteal artery. This was surgically repaired on April 27 with an uneventful postoperative course. Although the patient's rectal temperature generally remained below 100°F. during the period of penicillin therapy, and frequent blood cultures were negative, there was an occasional slight temperature rise. In addition, there were daily fluctuations of about 2°F. from the morning's low to the evening's high temperature, and there was a progressive loss of weight, continued elevation in the erythrocyte sedimentation rate, and persistent anemia in spite of numerous transfusions.

On the basis of these clinical findings, it was felt that active bacterial endocarditis was still present. Penicillin administration was stopped on May 7, and chloramphenicol therapy was begun. Within ten days there was a dramatic improvement in the patient's clinical appearance and the sedimentation rate and temperature became normal. The anemia, however, became more severe, and it was thought that the chloramphenicol might be a contributing factor. Chloramphenicol therapy was stopped on June 21. On June 26, the differential white blood cell count showed a marked shift to the left in the polymorphonuclear series, with 38 per cent neutrophils, 9 per cent metamyelocytes, and 2 per cent myelocytes. There were 8 nucleated red blood cells per 100 white blood cells. A rapid increase towards normal occurred in the patient's erythrocyte count, hemoglobin, and hematocrit during the following weeks. The blood cultures remained negative until a culture taken on July 24 grew a nonhemolytic *Staphylococcus aureus* in one of three flasks. Although it was later felt that this was probably a contaminant, streptomycin and Terramycin therapy was begun on Aug. 2. Once the antibiotic therapy had been started, it was felt that a full course of treatment should be completed, although all subsequent blood cultures were negative and the patient showed steady improvement. All antibiotics were discontinued on Sept. 23. The patient felt well and had gained weight, from 129 pounds to 158 pounds, by the time he was discharged from the hospital on Oct. 25. In April 1953, the patient was still asymptomatic and his weight was 192 pounds.

CASE 3.—A 21-year-old Negro developed anorexia, nausea, vomiting, chills, fever, and a cough on Nov. 15, 1950, while aboard an Army transport. Generalized weakness, myalgia, and headache followed. He slowly developed pain in the region of the left hip. Examination on Nov. 19 revealed a temperature of 103°F. and diminished breath sounds at the lung bases. The leucocyte
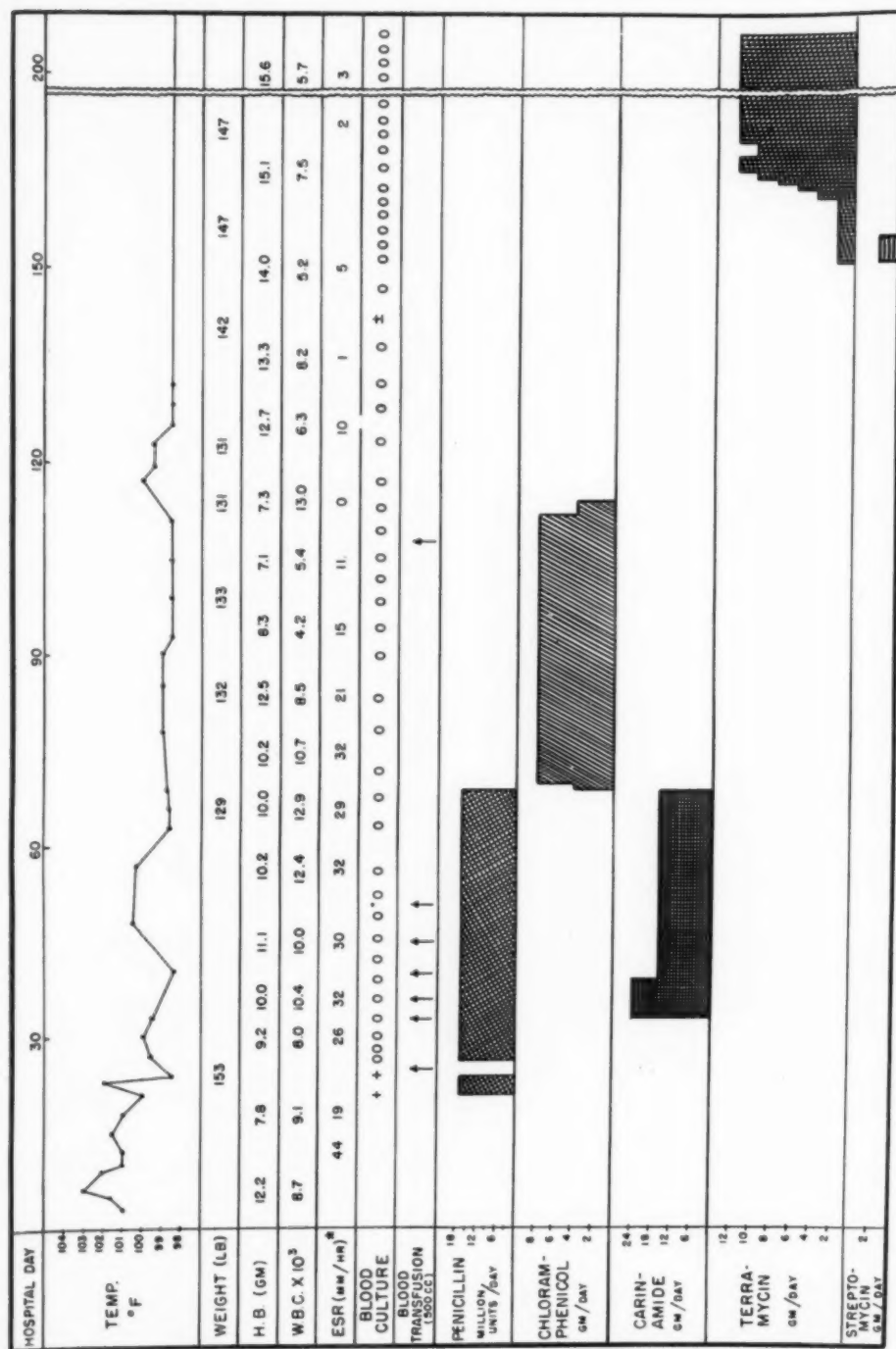
Fig. 2.—Clinical course of a patient (Case 2) with hemolytic *Staphylococcus aureus* endocarditis. For details, see text.

count was 24,800, with 81 per cent neutrophils.   The patient was treated with 300,000 units of penicillin and 4 Gm. of aureomycin daily.   He continued to be febrile and was transferred to Letterman Army Hospital on Nov. 21.   His previous health had been excellent.

On admission to this hospital the patient appeared toxic and acutely ill.   His weight was 160 pounds, temperature 105°F.; pulse, 120; respirations, 22; and blood pressure 80/50 mm. Hg.   The skin over the antecubital veins showed considerable punctate scarring.   A splinter hemorrhage was noted in the nailbed of the fourth left finger.   The heart was not enlarged, but a rough apical systolic murmur with a musical overtone was present.   Moderate tenderness was found in the right upper quadrant of the abdomen, but the liver and spleen were not palpable.   There was deep tenderness about the region of the left hip.   Recent self-administration of heroin by the intravenous route was suspected and later confirmed.

Laboratory findings: The leucocyte count was 12,250 with a differential count of 65 per cent segmented neutrophils, 17 per cent nonsegmented neutrophils, 7 per cent lymphocytes, 10 per cent monocytes, and 1 per cent eosinophils.   The erythrocyte sedimentation rate (Wintrobe) was 26 mm. per hour, and the hematocrit 42 per cent.   Urinalysis showed a trace of albumin, many white blood cells, rare red blood cells, and occasional granular casts.   A blood culture grew numerous colonies of hemolytic *Staphylococcus aureus* which were mannite and coagulase positive. The blood nonprotein nitrogen was 38 mg. per cent.   A serologic test for syphilis was negative. The electrocardiogram was normal.   Roentgenograms of the chest and hips were normal.

Hospital course: The administration of antibiotics had been discontinued upon admission of the patient to the hospital.   The systolic murmur present at the cardiac apex became rougher and louder.   On Nov. 23, after the first positive blood culture was reported, antibiotic therapy was resumed with the patient receiving 200,000 units of aqueous penicillin intramuscularly every two hours.   On Nov. 25, dullness, increased breath sounds, and a friction rub were noted at the right lung base.   Roentgenograms showed shadows of increased density in the lower and middle lobes of the right lung.   Initial in vitro studies showed inhibition of growth of the organism by 1 μg of Terramycin or aureomycin per c.c., but lack of inhibition by 1 unit of penicillin per c.c.   On Nov. 25, treatment with penicillin was replaced by the administration of 4 Gm. of Terramycin daily (Fig. 3).   The patient showed no evidence of improvement and developed increasing weakness.   On Nov. 28 Terramycin therapy was replaced by the use of 4 Gm. of aureomycin, 12 Gm. of sulfadiazine, and 12 Gm. of sodium bicarbonate daily.   A chest roentgenogram on Nov. 30 showed generalized cardiac enlargement, inflammatory infiltrations at both lung bases, and a small right pleural effusion.   Streptomycin, 0.5 Gm. every six hours, was added to the regimen on Nov. 30.   The following day dependent edema was noted, and the administration of sulfonamides and sodium bicarbonate was discontinued.   A low-sodium diet was instituted, the patient was digitalized, and injections of mercaptomerin sodium were given.   Edema disappeared promptly.

Sensitivity studies indicated that the organism obtained on Dec. 1 was inhibited by the combination of 5 units of penicillin and 15 μg of streptomycin per c.c.   The administration of penicillin, one million units every two hours, was started on Dec. 2.   The use of aureomycin was discontinued on Dec. 4.   On Dec. 11 the streptomycin dose was increased to 1 Gm. every 12 hours.   Several blood cultures taken during this period were positive.

The organism obtained on Dec. 18 was not inhibited in vitro by the combination of 50 units of penicillin and 15 μg of streptomycin per c.c., but zones of inhibition were obtained with aureomycin, Terramycin, chloramphenicol and bacitracin using the disc-sensitivity method.

On Dec. 21 therapy with streptomycin and pencillin was replaced with 1 Gm. of Terramycin every six hours.   The dosage was increased two days later to 2 Gm. every six hours.   Three consecutive sterile blood cultures were obtained.   On Dec. 31 the patient again had chills and fever.   Blood cultures again became positive.   Persistent anemia necessitated repeated blood transfusions.

The organism obtained on Dec. 22 was inhibited by the combination of 150 μg each of sulfadiazine, sulfamerazine, and sulfathiazole per c.c.   Treatment was supplemented during a five-day period by 6 Gm. of each sulfonamide given daily with added sodium bicarbonate.   Generalized edema developed.   The organism obtained on Jan. 8 was insensitive to sulfonamides but retained detectable sensitivity to Terramycin, aureomycin, chloramphenicol, and bacitracin.
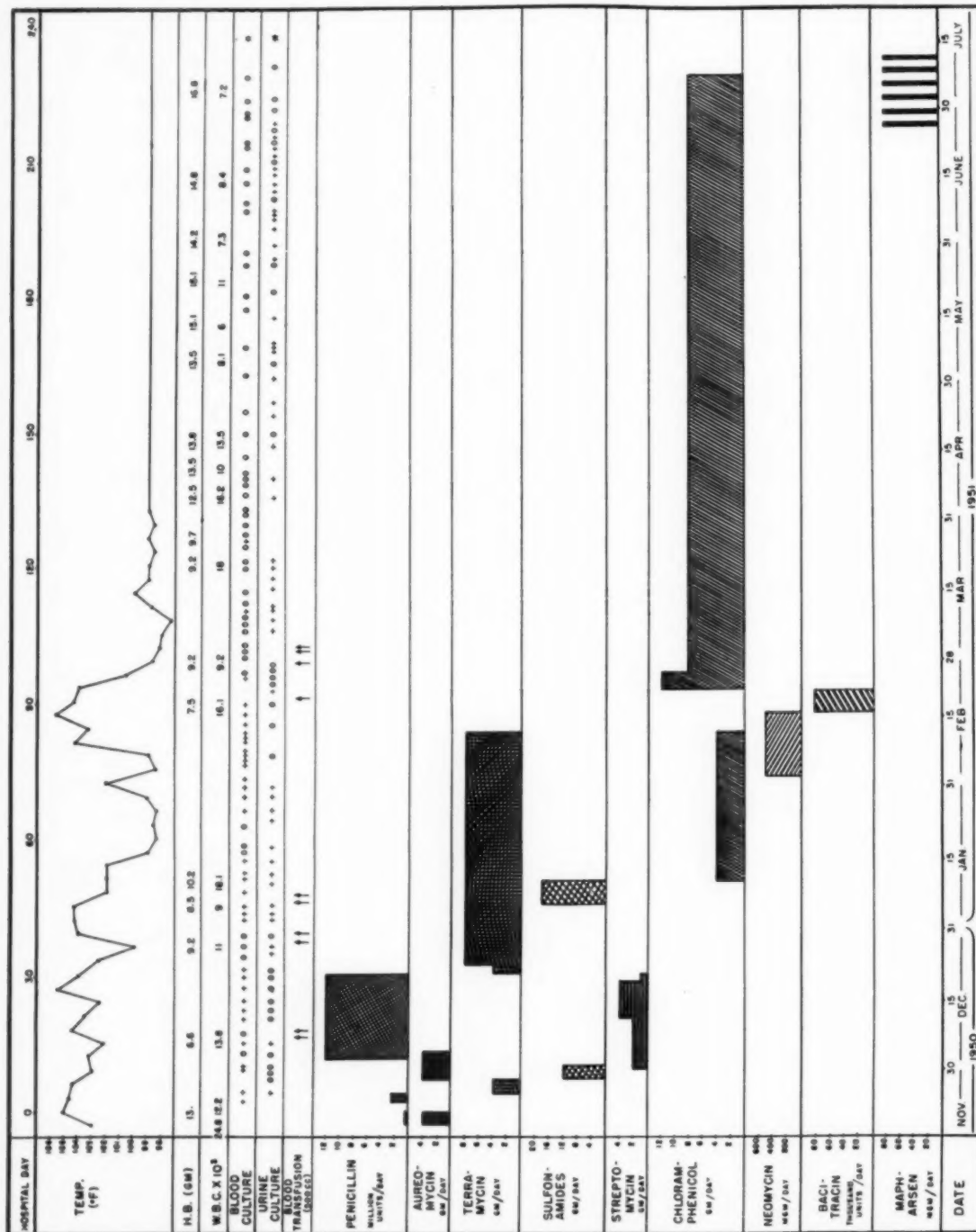
Fig. 3.—Clinical course of Case 3. The favorable response of the patient to chloramphenicol therapy after unsuccessful trial of other antibiotics is apparent. *Six additional cultures were negative.

On Jan. 10 the administration of 1 Gm. of chloramphenicol every six hours was added to the Terramycin therapy.   The patient became afebrile for the first time and two negative blood cultures were obtained by Jan. 18.   Urine cultures, however, remained persistently positive for hemolytic or nonhemolytic *Staphylococcus aureus*.   Following the reinstitution of intramuscular mercurial diuretics, the weight dropped to 112 pounds, and the edema disappeared.   On Jan. 30 the patient had chills and fever, and positive blood cultures were again obtained.

Additional in vitro studies indicated that the organism now was not inhibited by 50 µg of Terramycin or aureomycin per c.c. but was inhibited by 5 µg of neomycin per c.c.   Treatment with 167 mg. of neomycin every eight hours for 14 days was without appreciable effect.   By this time the patient had developed severe alopecia.   His weight had fallen to 106 pounds.   Anemia, fever, and vomiting persisted.   The heart murmur became very loud and was audible throughout the thorax and abdomen.   Chloramphenicol and Terramycin therapy were discontinued on Feb. 12.   A total of 400,000 units of bacitracin was administered intramuscularly from Feb. 16 to 21 but seemed to have no appreciable effect on his downhill course.   Transient albuminuria and elevation of the blood nonprotein nitrogen occurred.

At this time it appeared that administration of an unusually large dosage of an antibiotic showing some in vitro effect was the only remaining resource.   Therapy with 2 Gm. of chloramphenicol every four hours was started on Feb. 21.   The patient became moribund with absent deep tendon reflexes, and feeding by nasal tube was required.   The oral temperature varied between 96.2° and 97.6°F. on Feb. 24.   The following day the dosage was decreased to 2 Gm. every six hours, and thereafter gradual improvement began.   The anemia improved and the patient gradually began to gain strength and weight.   We were able to discontinue dietary salt restriction and the use of mercurials.   Most of the blood cultures between Feb. 24 and March 26 and all 39 blood cultures taken thereafter were sterile.   By mid-April the patient was ambulatory, the systolic murmur had decreased in intensity, and the hematocrit had risen to 45 per cent.   By May the sedimentation rate had returned to normal.   Urine cultures continued to show *Staphylococcus aureus* as well as occasional *Proteus vulgaris* or yeasts.   Repeated microscopic urinalyses showed only rare white blood cells.   An intravenous pyelogram was normal.   Beginning on June 26 the patient was treated with 60 mg. of Mapharsen intravenously every three days for six injections.   The fifteen urine cultures subsequently obtained failed to demonstrate staphylococci. The administration of chloramphenicol was discontinued on July 8.   The maintenance dosage of digitoxin was stopped on Aug. 4, 1951.   At that time the patient weighed 151 pounds and appeared to be in good health.   The only abnormality detectable was a soft systolic murmur with maximal intensity in the fourth intercostal space at the left border of the sternum.   The electrocardiogram was normal.   Roentgenograms showed residual pleural reaction at both lung bases but no cardiac enlargement.   The patient was still asymptomatic in January 1953, eighteen months after being discharged from the hospital.

<div align="center">DISCUSSION</div>

In the past, endocarditis caused by hemolytic *Staphylococcus aureus* was generally an acute, fulminating disease.   The clinical course of the disease, however, has been so greatly altered by the use of antibiotics that it is now often impossible to determine whether a particular case should be classified as "acute" or "subacute" bacterial endocarditis.[7]   We have, therefore, not attempted to differentiate our cases of endocarditis into the acute or subacute forms.

The three cases presented were all cured of their staphylococcus endocarditis. In Case 1, where the infecting organism was sensitive to penicillin and aureomycin, cure was readily achieved with these antibiotics.   In Case 2 sensitivity tests indicated that the organism was only partially inhibited by 15 units of penicillin per c.c.   Although no positive blood cultures were obtained while the patient received penicillin and carinamide therapy, the persistence of an elevated

Fig. 3.—Clinical course of Case 3.   The favorable response of the patient to chloramphenicol therapy after unsuccessful trial of other antibiotics is apparent.   *Six additional cultures were negative.

erythrocyte sedimentation rate, progressive cachexia, and anemia as well as fluctuations of about 2°F. in the daily temperature all suggested strongly that active bacterial endocarditis was still present. A course of chloramphenicol was then given. Within 10 days the patient's temperature and the erythrocyte sedimentation rate became normal, and there was marked improvement in the clinical appearance. Another organism recovered from culture of the patient's blood four weeks after cessation of chloramphenicol therapy was apparently a contaminant.

Case 3 presented a complex therapeutic problem necessitating the use of many antibiotics until a cure was finally obtained. Early in the course of therapy in this case, the infecting organism was inhibited in vitro by 5 units of penicillin combined with $15\mu g$ of streptomycin per c.c. After 18 days of streptomycin and 17 days of penicillin therapy, the staphylococcus recovered from the blood was not inhibited by 50 units of penicillin plus $15\mu g$ of streptomycin per c.c. Frequent sensitivity studies performed during the patient's illness also demonstrated the development of bacterial resistance to the sulfonamides, aureomycin, and Terramycin after these drugs were used. Attempts to achieve a cure with neomycin and bacitracin were ineffective in the dosage used. Massive (up to 12 Gm. per day) doses of chloramphenicol were then employed successfully.

Although chloramphenicol at times may produce bone marrow depression, it is interesting to note that concomitant with the cure of bacterial endocarditis in Case 3, there was a marked regeneration of the blood cell elements in spite of the unusually large doses of chloramphenicol being used.

Although we cannot be certain that cure in our second case was due to chloramphenicol, the marked clinical improvement, observed after this drug was administered, strongly suggests this effect. In Case 3, a cure was obtained with chloramphenicol after the unsuccessful use of penicillin, streptomycin, sulfonamides, aureomycin, Terramycin, neomycin, and bacitracin.

It is not intended to convey the impression that the use of chloramphenicol is generally preferable to any other antibiotic in treating staphylococcus endocarditis. We were able to find in the literature only two cases of staphylococcus endocarditis treated with chloramphenicol[8,9] with one cure.[9] No doubt numerous unreported cases have received this drug. However, the paucity of reports on the subject suggests caution in concluding that results have been especially favorable. Since chloramphenicol, like the sulfonamides, aureomycin, and Terramycin, is primarily a bacteriostatic agent, it would be anticipated that cures of bacterial endocarditis with chloramphenicol are difficult to achieve.

In general, penicillin remains the drug of choice in cases of staphylococcus endocarditis even with moderately resistant organisms[7] because of its low toxicity, wide range of dosage, and the high blood levels which may be achieved, particularly if therapy is supplemented by carinamide or benemid. We should like to emphasize the importance of frequent determinations of the sensitivity of the organisms recovered from the blood stream during therapy of bacterial endocarditis. Although in-vitro sensitivity studies do not directly parallel clinical effects, sensitivity tests do provide a guide to the intelligent choice of antibiotics to be used and the dosage requirements. Furthermore, the development of

bacterial resistance in the course of therapy, as shown in Case 3, is not unusual.[10] In resistant cases where there is a persistent endocarditis and bacteremia, the frequent performance of sensitivity tests using a variety of antibiotics alone and in combinations provides invaluable information in preventing prolonged efforts to cure a serious infection with an ineffective antibiotic.

SUMMARY

Three cases of hemolytic *Staphylococcus aureus* endocarditis are reported. One patient was cured with penicillin and aureomycin while the other two patients responded favorably to chloramphenicol.

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Clinical Reports

THE WOLFF-PARKINSON-WHITE SYNDROME ASSOCIATED WITH PAROXYSMAL VENTRICULAR TACHYCARDIA

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IN 1930 Wolff and associates[1] reported the unusual electrocardiographic pattern of short P-R interval and apparent bundle branch block in healthy young individuals subject to frequent attacks of paroxysmal tachycardia. Wilson (1915),[2] Wedd (1921),[3] and Hamburger (1929)[4] reported cases with similar electrocardiographic patterns; however, the benign nature and significance of this condition were not well recognized until 1930. In 1939 Hunter and associates[5] reviewed the literature, collecting ninety cases and adding nineteen original cases. Electrocardiograms were available during paroxysms of tachycardia in seven cases. In five supraventricular tachycardia was recorded, in one supraventricular and ventricular tachycardia and in the remaining case auricular fibrillation and ventricular tachycardia were found. Levine and Beeson[6] reported three cases of the Wolff-Parkinson-White syndrome associated with attacks of paroxysmal ventricular tachycardia. Palatucci and Knighton,[7] Fleischman,[8] and Klainer and Joffe[9] added three additional cases of paroxysmal ventricular tachycardia occurring with this syndrome. The episodes of paroxysmal rapid heart action occurring in cases of Wolff-Parkinson-White syndrome are most commonly auricular tachycardia, occasionally auricular fibrillation, and rarely ventricular tachycardia. Thus, we have been able to find in the literature only eight cases of Wolff-Parkinson-White syndrome associated with paroxysms of ventricular tachycardia. In view of the rarity of this combination, our cases are presented.

CASE REPORTS

Case 1.—The patient, a 22-year-old Negro, was admitted to the United States Army Hospital, Fort Benning, Ga., on Oct. 30, 1951 complaining of "palpitations". He was apparently well until one and one-half hours prior to admission, at which time, while playing billiards, he was pushed by a friend and then noted the onset of palpitation. There was no dyspnea or chest pain at the onset; however, shortness of breath gradually developed. Profuse sweating, weakness, and dizziness were prominent symptoms. Two to three weeks previously the patient had noted palpitation which was not particularly bothersome and which disappeared after a few minutes. His first attack occurred at the age of 15 while playing football, and other attacks continued to occur approximately once a month. They were invariably associated with physical

activity of the strenuous type, would last about 15 minutes, and disappear with rest.   He had the usual childhood diseases.   He contracted a Neisserian infection at 17 years of age but denied syphilis.   There was no history of rheumatic fever or severe infectious disease.   Family history revealed an uncle who had hypertension and heart disease.

Physical examination revealed a very well developed and well nourished Negro in acute distress.   He was dyspneic, perspiring profusely, and complained of marked weakness and dizziness.   Temperature was 98.6° F., radial pulse rate of 190 to 200 per minute.   Eyes, ears, nose, and throat were normal.   The neck veins were not distended, and the lungs were normal to auscultation and percussion.   Examination of the heart revealed a rate of 200 per minute with slight irregularity.   There was marked changing intensity of the first heart sound.   No thrills or murmurs were noted.   Blood pressure was 110/80 mm. Hg, the pulse was weak and thready at the wrist.   The remainder of the physical examination was essentially negative.
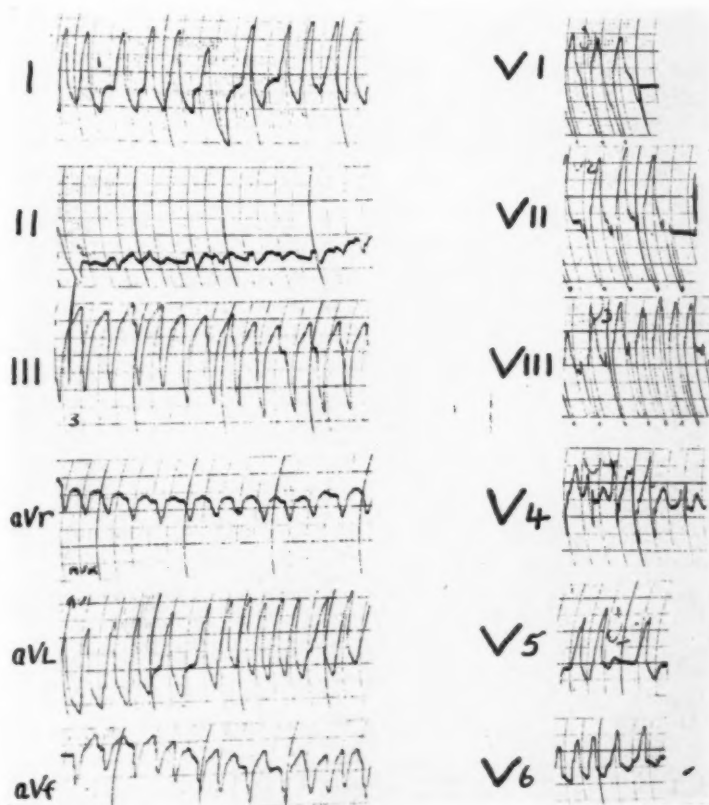

Fig. 1 (Case 1).—Initial electrocardiogram demonstrating ventricular tachycardia at a rate of 200 beats per minute.

Laboratory data included the following: White blood count, 7,800 per cu. mm.; neutrophils 48 per cent; lymphocytes 50 per cent; and monocytes 2 per cent; hemoglobin 14.7 Gm. (Sahli); sedimentation rate 2 mm. per hour (Wintrobe); hematocrit 52 per cent; urinalysis was normal; the Wassermann serologic test for syphilis was negative; total cholesterol was 230 mg. per cent; the total protein was 7.7 Gm. per cent, albumin 4.4 Gm., and globulin 3.3 Gm.   Roentgenogram of the chest showed clear lung fields and a heart that was normal in size and configuration.

Initial electrocardiogram (Fig. 1) revealed paroxysmal ventricular tachycardia.   The patient was given morphine sulfate, ¼ grain subcutaneously, and 3 grains of quinidine sulfate orally.

This dose of quinidine was repeated in 15 minutes. He was given 6 grains of quinidine orally one-half hour later. One and one-half hours after initiation of therapy and after a total dose of 12 grains of quinidine, the electrocardiogram (Fig. 2) revealed a conversion to sinus tachycardia, and soon after to sinus rhythm. At this point the patient became almost entirely free of symptoms. The resting electrocardiogram revealed a short P-R interval (less than 0.10 sec.) and a widened QRS complex (0.12 to 0.14 sec.) with slurring of the QRS complexes and in many leads, T waves opposite in deflection to that of the QRS. Two weeks later 1/30 grain of atropine sulfate was given subcutaneously in an attempt to decrease vagal tone and to abolish the Wolff-Parkinson-White syndrome. There resulted a sinus tachycardia (Fig. 3) with widening of the P-R interval to 0.12 sec. and decreasing the QRS duration to 0.08 sec. In addition the T waves throughout the precordial leads became inverted. These electrocardiographic changes disappeared when the physiologic action of atropine waned. During the hospital stay, the patient received 3 grains of quinidine sulfate orally three times daily with no recurrence of palpitation.
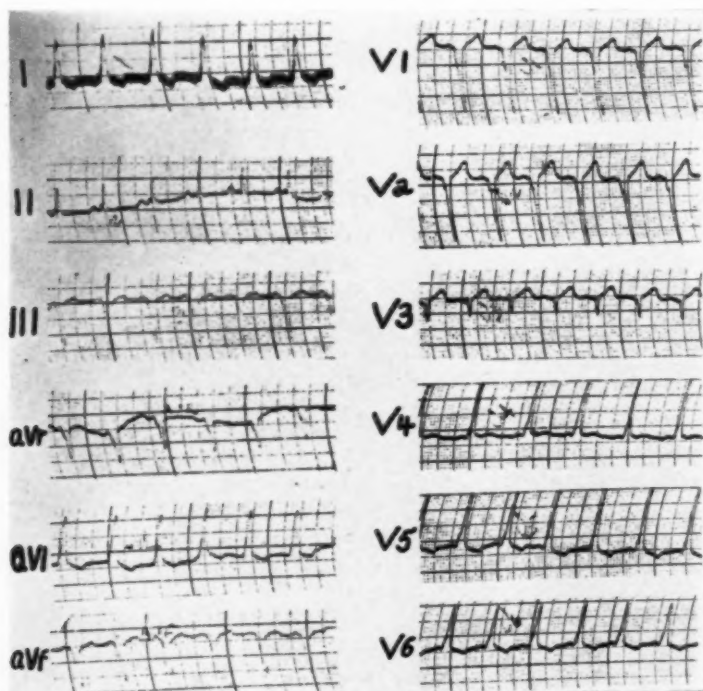

Fig. 2 (Case 1).—After 12 grains of quinidine the electrocardiogram reveals regular sinus tachycardia at a rate of 100. The Wolff-Parkinson-White syndrome is now noted.

CASE 2.—A 26-year-old Negro came to the emergency room of the United States Army Hospital, Camp Gordon, Ga., at 7 A.M., Jan. 15, 1953, complaining of "shortness of breath on walking, jumping of my stomach, and my heart skips." He was entirely well until nine hours prior to hospitalization when he suddenly awoke from a sound sleep with a feeling of smothering. He had been asleep only about 15 minutes when this occurred. The patient considered the cause to be, "Gas on my stomach from eating chile." He had taken baking soda and vomited without relief. Dyspnea was most noticeable when he attempted to walk. He propped himself up on two pillows and finally fell asleep about four hours before admission. Because of dyspnea on walking, he reported to the hospital instead of going to work.

Past history was essentially negative. He had been in the army continuously for thirty-one

months, up to the time of admission, and had had no serious illnesses.   His only hospitalization was for wounds of the left leg received in Korea.

On physical examination he appeared to be an anxious, fatigued, but otherwise healthy, well-developed Negro.   Respirations were 16 to 24 per minute, temperature 98.4° F., and blood pressure 126/80 mm. Hg.   The pulse was very rapid, irregular, varied greatly in quality, and changed so rapidly that the rate could not be counted accurately.   The significant physical findings were limited to the heart.   There was no enlargement to percussion, and no murmurs were heard.   The apical heart rate appeared grossly irregular with paroxysms of rapid, regular rhythm at a rate well over 200 beats per minute.   Carotid sinus pressure and orbital pressure had no effect.
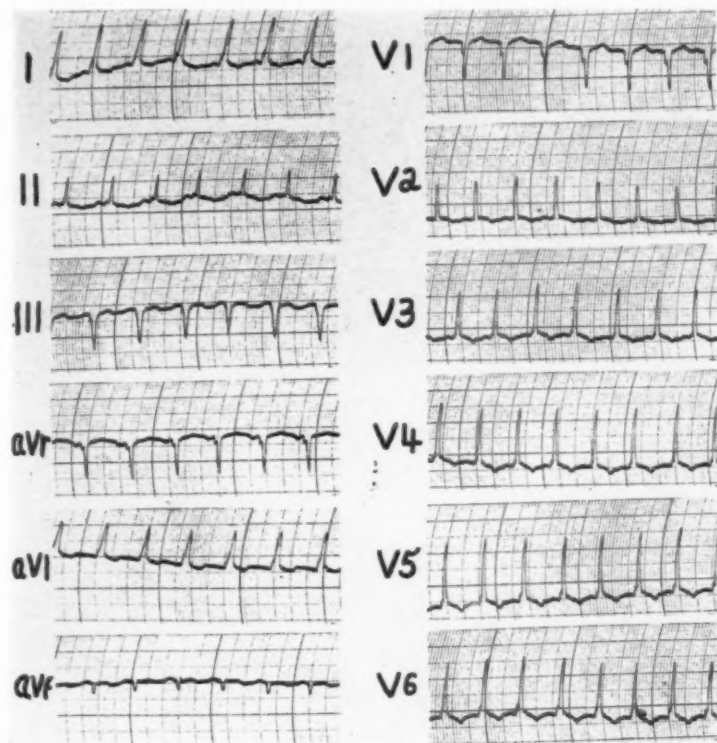

Fig. 3 (Case 1).—After atropine (1/30 grain) subcutaneously. The Wolff-Parkinson-White pattern is no longer present, and the heart rate has increased to 125 beats per minute.

Laboratory data included: Urinalysis, complete blood count, and roentgenogram of the chest were within normal limits.   An electrocardiogram (Fig. 4) demonstrated paroxysmal ventricular tachycardia, with a rate of 260 per minute, and short runs of nodal tachycardia.   The patient was given 300 mg. of procaine amide (Pronestyl) hydrochloride intravenously, and (Fig. 5) the rate decreased to 170 per minute.   Also, complexes of the Wolff-Parkinson-White type were interspersed between short runs of ventricular tachycardia.   Fifteen minutes later 300 mg. of procaine amide hydrochloride were again given intravenously and the rate slowed to 148 per minute.   At this time (Fig. 5) the short P-R interval with widened and slurred QRS complexes (Wolff-Parkinson-White syndrome) is more readily visible.   About 15 minutes later a repeat dose of procaine amide hydrochloride, this time 400 mg., decreased the rate to 135 beats per minute.   Wolff-Parkinson-White complexes with infrequent short runs of ventricular tachycardia, nodal tachycardia, and an occasional apparently normal sinus beat were noted.

Since no more intravenous procaine amide hydrochloride was available, 500 mg. were given orally, but with no further electrocardiographic change. Three hours later, quinidine sulfate, 3 grains, was given by mouth. Two hours later the electrocardiogram was unchanged, hence 6 grains of quinidine were administered. Twenty minutes later he vomited. An hour later the electrocardiogram was unchanged, hence 10 grains of quinidine were administered orally. One hour after this the radial rate was 83 per minute, and a normal sinus rhythm resulted (Fig. 6). The typical Wolff-Parkinson-White syndrome is evident as manifested by the short P-R interval (0.04 to 0.08 sec.) and the slurred, notched, widened (0.10 to 0.12 sec.) QRS complexes. Quinidine therapy was discontinued with no recurrence of tachycardia during hospitalization.
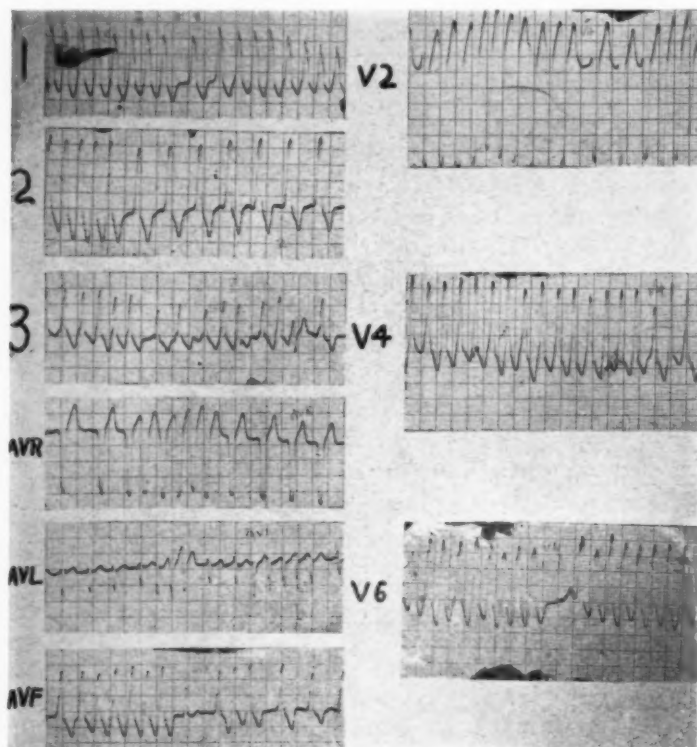

Fig. 4 (Case 2).—Paroxysmal ventricular tachycardia at rate of 260. Note several Wolff-Parkinson-White complexes in Lead II and short bursts of nodal tachycardia in lead aV_L.

DISCUSSION

The characteristic electrocardiographic pattern of the Wolff-Parkinson-White syndrome consists of (1) a P-R interval of 0.1 sec. or less, and (2) a QRS duration of 0.11 sec. or more. The QRS complex is frequently slurred or notched, usually at the upstroke of the R wave or the downstroke of the S wave. In addition the T waves may be in opposite deflection to the QRS. This unusual electrocardiographic pattern often occurs in healthy young individuals with no clinical evidence of heart disease and whose only difficulty is their predilection to paroxysmal rapid heart action. It is of rather rare occurrence, for Hunter and associates[10] could demonstrate only eight cases constituting 5.7 per cent of 140 consecutive cases of bundle branch block, and 5.3 per cent of 150

consecutive cases of paroxysmal tachycardia. Although this syndrome has been well established to be benign in nature and probably a congenital anomaly, physicians may mistakenly diagnose true bundle branch block indicating organic heart disease to be present. When associated with ventricular tachycardia, severe myocardial disease must also be considered. Likewise, the widened and notched QRS complexes may mask an associated posterior wall myocardial infarction. When in addition auricular fibrillation is present with absence of P waves, it proves difficult to differentiate the widened QRS complexes of the Wolff-Parkinson-White syndrome from those due to ventricular premature contractions. Those cases found associated with organic heart disease have been considered coincidental.
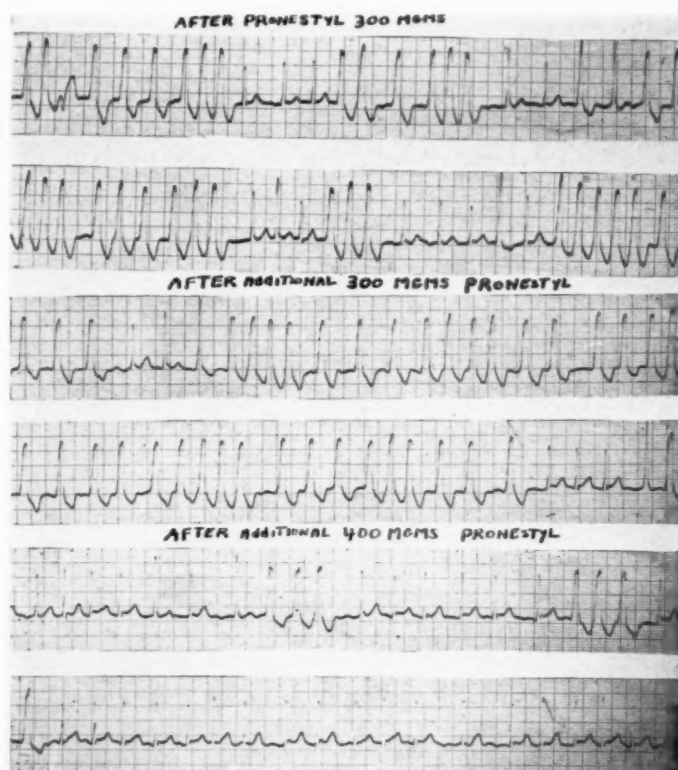
Fig. 5 (Case 2).—Electrocardiogram demonstrating the effect of intravenous Pronestyl.

The mechanism responsible for the Wolff-Parkinson-White syndrome is not known. Holzman and Scherf,[11] and Wolferth and Wood[12,13] presuppose an anomalous pathway (the so-called Bundle of Kent) for the conduction of the sinus impulses from atria to ventricles by-passing the atrioventricular node. Such an aberrant muscular connection between atria and ventricles was demonstrated post mortem[14] in a case of the Wolff-Parkinson-White syndrome who died in paroxysmal tachycardia. The frequency of auricular tachycardia in these cases is thought by some to be due to retrograde conduction of sinus impulses along this aberrant pathway into the atrium.

Recently Prinzmetal[15] and his group have reproduced the Wolff-Parkinson-White syndrome in dogs by subthreshold electrical stimulation of the atrioventricular node. Modification of this current produced all the supraventricular arrhythmias associated with this syndrome. Cutting the Bundle of His prevented development of the Wolff-Parkinson-White complexes, thus ruling out, in the dog at least, the passage of the impulse over the Bundle of Kent. Cinematography suggests that slurred upstroke of the R wave was caused by an early localized contraction in one ventricle.
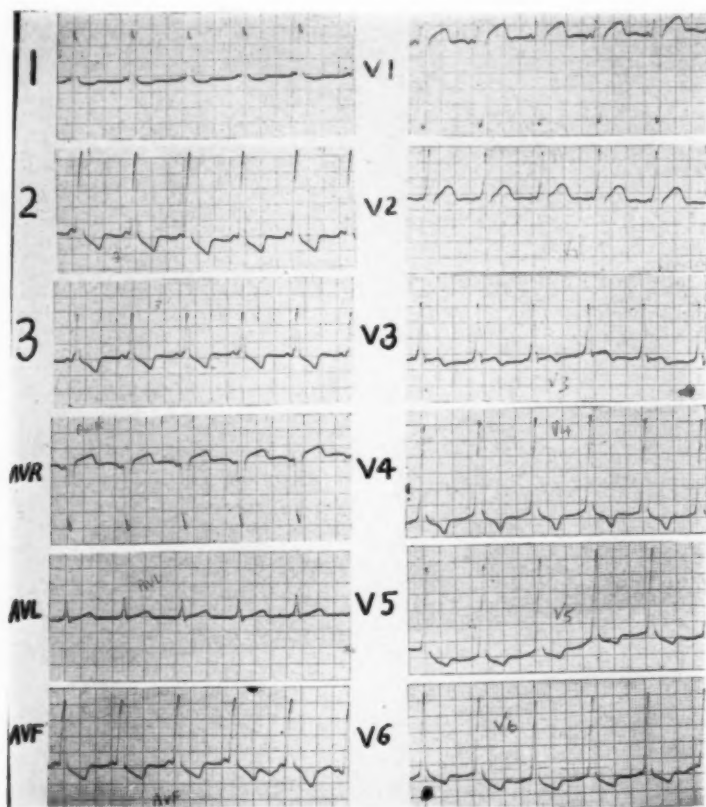
Fig. 6 (Case 2).—Regular sinus rhythm after 12 grains (0.8 gm.) quinidine revealing Wolff-Parkinson-White syndrome. P-R interval, 0.04 to 0.08 sec.; QRS interval, 0.12 sec. Low T₁, inverted T₂, and T₃. Upright T in aV_R. Inverted T in aV_F and V₃ to V₆. QRS complexes are slurred and notched.

The electrocardiographic pattern of short P-R interval and prolonged QRS duration may disappear spontaneously, after exercise, and with atropine, and may reappear on vagal stimulation by carotid sinus pressure, digitalis, or cholinergic drugs (Prostigmin, Mecholyl, etc.).[16] Quinidine has been effective in abolishing the abnormal pattern.[17]

Our cases demonstrate the classical electrocardiographic pattern of short P-R interval and apparent bundle branch block. The patients were in acute distress and the ventricular tachycardia responded well to oral quinidine in the

first case and to combined procaine amide hydrochloride and quinidine therapy in the second case. In the first case, atropinization caused a sinus tachycardia and lengthened the P-R interval and decreased the QRS duration, but in addition caused widespread inversion of T waves in the precordial leads. We feel that the latter finding is due to a temporary myocardial anoxemia secondary to the rapid heart rate. Despite the apparent benign nature of this syndrome it is necessary to treat the associated paroxysmal tachycardia vigorously for patients have succumbed during such episodes.

SUMMARY

Two cases of the Wolff-Parkinson-White syndrome associated with paroxysmal ventricular tachycardia are recorded with a review of the pertinent literature.

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CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION SECONDARY TO NONPENETRATING INJURY OF THE CHEST WALL

HAROLD J. LEHMUS, M.D., ALFRED B. SUNDQUIST, M.D., AND LANE W. GIDDINGS, M.D.

MANCHESTER, CONN.

T HE medicolegal implications of trauma and heart disease are great. Until recently the relation of nonpenetrating injuries to the chest and injury to the heart and its related structures has been overlooked. Many authorities agree that injuries to the epicardium, myocardium, and valves may occur as the result of injury to the chest.[1-3] Others[4,5,10] feel, however, that this evidence is still far from conclusive, and much remains to be done to establish the relationship. There are surprisingly few reports of coronary thrombosis with myocardial infarction following chest trauma that can be substantiated without question. The following case presents such a striking sequence of events that the time relationship of a direct injury to the chest and coronary thrombosis with resultant death could not be overlooked.

CASE REPORT

A 62-year-old white farm laborer was admitted to Manchester Memorial Hospital at 10:50 A.M. on Aug. 25, 1951 and died at 1:10 P.M. on the same day, two hours and twenty minutes after admission. Between 9:30 and 10:00 A.M. of the same morning he had been a front-seat passenger in an automobile which was involved in a collision with another car. He apparently had been thrown against the dashboard of the vehicle and then out of the car. At the time of admission he complained of severe pain in the right anterior chest and the right hip. Examination showed tenderness of the right lower thoracic cage in the midaxillary line. There were pain and tenderness in the right hip region and the impression on admission was that he had multiple fractures. Within 15 minutes roentgenograms were made of the patient, and the wet films were negative for fractures. At 11:15 A.M. the patient began complaining of pain in the substernal region and particularly in the third intercostal space to the right of the sternum where a small contusion was found. At 11:20 A.M. the patient was admitted to the ward complaining of severe substernal constriction and could not get comfortable in bed. He was given $\frac{1}{4}$ grain morphine sulphate subcutaneously but received only slight relief. His heart sounds were of good quality, blood pressure 180/110 mm. Hg and his color was good. He began to complain of difficulty in breathing and at 11:45 A.M. he was given 1/6 grain morphine and put into an oxygen tent. The patient became extremely apprehensive and restless and fought the oxygen tent so that at 12:20 P.M. he was given another $\frac{1}{4}$ grain of morphine, but his color and respiration became progressively worse and he expired at 1:10, approximately 3 to $3\frac{1}{2}$ hours after the automobile accident.

Past history was learned from acquaintances of the patient. In 1929 he had a "nervous breakdown," and he had a "stroke" with paralysis of one lower extremity from which he recovered. In 1944 to 1945 he was treated at the Johns Hopkins Hospital and the Mayo Clinic for "trigeminal neuralgia."

At times recently he complained of dyspnea and of being unable to move a wheelbarrow up a hill despite the fact that he worked long hours doing usual farm labor every day. He took large doses of phenobarbital. Two to three weeks prior to the accident he woke up at midnight feeling "chills" and pains in his chest. On the day of the automobile accident he was on his way to see a physician for treatment of a finger which he had cut two to three weeks prior to admission. Nothing else could be learned of this patient's past history.

Some of his working associates were questioned and it was learned from them that he was a hard worker and did heavy manual labor.

<div align="center">POST-MORTEM FINDINGS</div>

GROSS EXAMINATION   (Restricted to the significant findings).—

Pericardial cavity: A small amount of clear serous fluid is present. The entire inner lining surface of the pericardial sac appears grey-white, smooth, and glistening.

Heart: The heart weighs 350 grams with a large uniformly red softened area involving three-fourths of the wall of the anterior and lateral left ventricles. Moderate myocardial thickening is present, and the endocardium appears slightly grey and fibrous. The heart valves show some fibrous thickening but otherwise are relatively normal.

Coronary vessels: The vessels are hard and brittle and "pipe-stem" in consistency. Sectioning shows marked atheromatous thickening and narrowing of the lumina. Tracing down the left anterior descending coronary branch, serial sections show occlusions at the point of narrowing and a hemorrhage into the wall with a small red fibrinous thrombus blocking the lumen.

MICROSCOPIC EXAMINATION   (Also restricted to significant findings).—

Heart: Sections from the red infarcted area show a thickened wall containing swollen muscle fibers with vacuolated cytoplasm and a fused hyalin appearance with absent striations. The interstitial connective tissue stroma shows hemorrhagic congestion with infiltration by large numbers of red blood cells. The inflammatory process appears early and only an occasional polymorphonuclear cell is observed.

Coronary vessels: Sections of these vessels at the site of occlusion show marked atheromatous thickening of the intima and media with calcific deposits and vacuolated areas of cholesterol deposition which in some foci show asteroidlike cholesterol crystals and in some foci are filled with red blood cells. Marked annular hemorrhage at the periphery of the media, characteristic of fresh coronary occlusion, is present. At one point in the lumen a fibrin-type thrombus is adherent. The endothelial cell lining is interrupted and the broken edges extend up into the overlying thrombus. Moderate numbers of red blood cells are present in the base of the thrombus which extends into a subjacent atheromatous area in the media.

Diagnoses: (1) Coronary thrombosis and medial hemorrhage, fresh, left anterior descending coronary branch; (2) left myocardial infarction, large, recent; (3) chronic coronary atherosclerosis, marked.

<div align="center">COMMENT</div>

No doubt in this case the fundamental cause of coronary thrombosis is atherosclerosis of the coronary vessels, but the time relationship and the sequence of events following the blunt type of injury to the anterior chest wall and the postmortem findings of subendothelial hemorrhage and fresh thrombosis of not more than several hours' duration cannot be overlooked. There are instances where a blunt injury to the chest wall apparently precipitated in atherosclerotic coronary arteries occlusion and myocardial infarction. The injury to the heart may occur indirectly from transmitted forces especially against the thorax, but apparently it may be transmitted from other parts of the body as well. These produce vibrations that indirectly injure the heart, the myocardium, or coronary arteries.[1,6]

Jokl and Greenstein[7] report the case of a 10-year-old boy who while boxing received a number of blows against the chest and abdomen and was knocked down but did not seem unduly distressed, although he died five minutes after a boxing match of three rounds. At autopsy the left descending branch of the coronary artery was blocked and there were slight atheromatous changes in the intima. A well-organized thrombus occupied most of the whole lumen of the vessel.

It has been felt by many that most cases of cardiac damage occur only in severe penetrating chest injuries and are fatal. Many cases of cardiac damage, including rupture of the heart, result from nonpenetrating chest injuries although the chest cage may remain intact without even a fractured rib.[8] Various arrhythmias including auricular flutter and fibrillation as well as transient and permanent varying degrees of heart block may occur.[1,8,9,12] Those that survive may recover completely or may remain with symptoms of angina or cardiac insufficiency. A latent period of days to months may follow and the cardiac injury may manifest itself at a later date either in an aneurysm or in congestive failure. Arenberg[8] presented twenty-eight cases of myocardial contusion with various cardiac disabilities following chest injuries. Most of the individuals were in their fifth and sixth decades, and he felt that damage was likely to occur from injury to a heart previously diseased. He points out that the severity of the chest trauma and the chances of cardiac damage do not necessarily correspond, and naturally there is a tendency for some injured patients to exaggerate symptoms for purposes of compensation.

Master[10] differentiates between acute coronary insufficiency which may be brought about by exertion, excitement, or trauma and acute coronary occlusion which he feels is a sequal of arteriosclerosis and is not precipitated by effort or excitement. He studied types of activity at the onset of coronary occlusion in 1,068 attacks. Only 2 per cent occurred with unusual or severe exertion. He also studied the role of occupation in acute coronary occlusion and in a series of 1,368 cases occlusion occurred with equal frequency in all occupational groups. He concluded that if coronary occlusion were precipitated by effort, the incidence in strenuous occupation should be greater, whereas actually the percentage of sedentary persons was the same as that of heavy laborers. In his discussion of the role of trauma in acute coronary occlusion, he points out that in most instances the authors fail to differentiate contusion of the heart from coronary occlusion. In many cases post-mortem examination was not made and a long interval had elapsed between the occurrence of the trauma and death and the pre-existing severe acute coronary artery disease which would suggest that the occlusion was not related to trauma. He does admit, however, that it is conceivable that a severe injury could contuse a coronary artery with resulting closure of the lumen and infarction of the ventricle. Boas[11] cites fourteen cases which warranted a conclusion that the syndrome of coronary occlusion may be induced by a nonpenetrating injury followed by unusual effort. When trauma or effort damages the heart, cardiac symptoms develop almost immediately with rare exceptions. There may be considerable variation in time before the full symptoms of incapacity develop. There may be a free interval of hours to days and on rare

cases even weeks. Boas feels that if the symptoms are immediately disabling, the causal connection is clear.

Levy[13] reported the case of a 49-year-old woman who was known to be hypertensive and had been observed. She was in an automobile accident and was thrown forcibly against the back of the front seat which resulted in a contusion of the anterior chest wall. She developed pain in the left anterior chest, difficulty in breathing and electrocardiographic changes were typical of acute myocardial infarction. Subsequent electrocardiographic changes showed evolution of this pattern and she died ten days later. Autopsy examination showed a large myocardial infarction comprising the anterior half of the interventricular septum and lower half of the anterior wall and entire apex. The left anterior descending artery was occluded completely by red and grey material, and there were atherosclerotic changes and hemorrhage into an atherosclerotic plaque of the left main coronary artery. He felt that vessels lying superficially on the muscle wall were subject to direct damage particularly when diseased and brittle.

SUMMARY

The case of a 62-year-old man is presented who expired a few hours after receiving a blunt type of chest injury and pathologic examination disclosed fresh coronary thrombosis and hemorrhage with myocardial infarction in blood vessels that showed marked coronary atherosclerosis. It is pointed out that pre-existing atherosclerosis of the coronary vessels may make these vessels particularly susceptible to injury from nonpenetrating trauma of the chest wall. In the discussion evidence is cited to establish the relationship of blunt type of chest injury and coronary thrombosis.

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Book Reviews

CIRCULATORY DYNAMICS. (No. 4, Modern Medical Monographs). Carl J. Wiggers. New York, 1952, Grune & Stratton, Inc. 107 pages.

The application of adequate methods for the measurement of intravascular pressures to the human being has greatly increased the need for understanding of the basic principles of instrumentation and of the physics of the circulatory system. As might have been predicted by the many cardiologists who are familiar with the contributions of Dr. Wiggers to circulatory physiology, this little monograph is concerned almost entirely with intra-arterial and intracardiac pressures. It does not pretend to discuss completely the complex inter-relations of blood flow, blood pressure, resistance, and elasticity throughout the vascular system. Neither does it include specific data on the output and size of the heart. The reader would probably have welcomed a summary of Wiggers' opinions respecting such additional data. Certainly, this comment reflects in no way on the value of the material which has been included in this monograph, but one may hope that Dr. Wiggers will address himself to the more comprehensive task of expanding this summary into a complete statement on "circulatory dynamics."

The understanding of the genesis and propagation of the pressure pulses is essential to the cardiologist and to all others who measure blood pressures. Wiggers illustrates most effectively that much more information is actually available in this study than that which is gleaned currently in conventional clinical measurements. Inferences from the contours, magnitudes, and propagation of the pressure pulses are remarkable for their accuracy concerning cardiac output, resistance to flow, distensibility of the aortic compression chamber, economy of cardiac effort, etc., even though direct data on blood flow are not available to complete the informational picture. It is indeed fortunate that this is the case since the technology of blood flow measurement is relatively not as far advanced in serving clinical needs as that of pressure measurement.

In the reviewer's opinion, the most interesting and valuable section of the monograph deals with the analysis of ventricular contraction under abnormal conditions. Employing pressure data, Wiggers describes in a pithy clear manner the role of filling, initial tension and length, myocardial contractility, and the sequence of fractionate contractions, in the ventricular performance in such conditions as pericardial effusion, hypervolemia, oligemia, arterial hypertension, aortic coarctation, aortic stenosis, pulmonary stenosis, aortic regurgitation, mitral insufficiency, mitral stenosis, and in several arrhythmias. These examples provide neat exercises for the application of basic physical principles. The reader will find in this discussion concepts which will aid significantly his practical approach to these frequently encountered conditions.

A.B.H.

ANGIOQUIMOGRAFIA. Ayres de Sousa. Lisboa, 1951, Livraria Portugália, 240 pages and 173 illustrations (English summary).

This monograph presents a new diagnostic procedure based on the taking of a roentgenkymogram of the chest after injection of a contrast substance. Using a single or double-slit kymograph, the author studied pulmonary circulation time, and the effect of respiration upon venous return, formation of stream lines, and venous pulsations.

The method is not difficult but requires special knowledge and equipment. Moreover, the use of a contrast substance represents a certain risk for the patient.

For the study of pulmonary circulation time, a single-slit kymograph was placed at the base of the cardiac pedicle.   Twenty cubic centimeters of solution were injected within two seconds in adults while the films were moving at 2 cm./sec.   The arrival of the contrast substance to the superior cava, pulmonary artery, and aorta, was timed in the film.

It is claimed that this method permits an accurate measurement of circulation time from right ventricle to left atrium.   In one normal individual, a circulation time of 4.5 seconds from cava to aorta was found.   The value of this technique is still not demonstrated even though a good point is made concerning its possible application.

Excellent pictures and diagrams are presented.

A. A. L.

CLINICAL DISORDERS OF THE HEART BEAT: Samuel Bellet, M.D., Philadelphia, 1953, Lea & Febiger, 373 pp.   Pr. $8.50.

This is probably the most complete book on this particular subject in English.   As a rule treatises on this phase of cardiology have consisted largely of discussion of the electrocardiographic findings.   The author in this volume deals with the whole subject.   Physiology and pathology are dealt with as well as the etiology, symptoms and physical findings in the various disorders.   There is a full electrocardiographic presentation accompanied by many excellent electrocardiograms to illustrate the different conditions.   A good discussion of treatment is also given and at the end of the book the drugs most commonly used are discussed in detail.   In other words, every phase of the individual disorder is fully presented.   There is a large bibliography appended, which will aid anyone interested in a particular phase.

The book is well and clearly written and can be highly recommended, not only to the cardiologist, but to all those interested in the medical aspects of disease.

J. H. C.

Announcement

The 1954 meeting of THE AMERICAN GOITER ASSOCIATION will be held at the Somerset Hotel, Boston, Massachusetts, April 29, 30, and May 1, 1954.   The program for the three day meeting will consist of papers and discussions dealing with the physiology and diseases of the thyroid gland.

Announcements

THREE POSTGRADUATE COURSES IN PEDIATRIC CARDIOLOGY are to be offered twice during 1954 by COOK COUNTY GRADUATE SCHOOL OF MEDICINE. They will be presented by Benjamin M. Gasul, M.D., Attending Pediatrician and Director of the Cardiac Division of the Cook County Children's Hospital, and Egbert H. Fell, M.D., Attending Surgeon, Cook County Hospital, and Associates.

The courses will be intensive and practical, and are designed for the pediatrician, internist, general practitioner and roentgenologist. Examination of patients and the detailed study of case histories will utilize the wealth of clinical material available.

Course I

The Diagnosis and Treatment of Congenital and Rheumatic Heart Disease in Infants and Children, one week, starting April 19 and Oct. 18, 1954.

Course II

Roentgenology and Electrocardiography in Heart Disease in Infants and Children, three days, starting April 26 and Oct. 11, 1954.

Course III

Angiocardiography and Catheterization of the Heart and Great Vessels in the Diagnosis of Congenital and Acquired Malformations in the Hearts of Infants and Children, three days, starting April 29 and Oct. 14, 1954.

For information, address: Registrar
707 South Wood Street
Chicago 12, Illinois

Dr. Samuel A. Levine, Clinical Professor, Harvard University Medical School, Boston, will take part in a CONTINUATION COURSE IN CARDIOVASCULAR DISEASES FOR GENERAL PHYSICIANS which will be presented at the Center for Continuation Study on the University of Minnesota Campus March 22 to 24, 1954. The course, sponsored jointly by the University and the Minnesota Heart Association, will stress management of practical problems in the cardiovascular field. Dr. Levine will also present the annual George E. Fahr lecture on March 23. The course will be presented under the direction of Dr. C. J. Watson, Professor and Head, Department of Medicine, University of Minnesota Medical School, and the remainder of the faculty will include clinical and full-time members of the faculty of the University of Minnesota Medical School and the Mayo Foundation. Lodging and meal accommodations are available at the Center for Continuation Study.